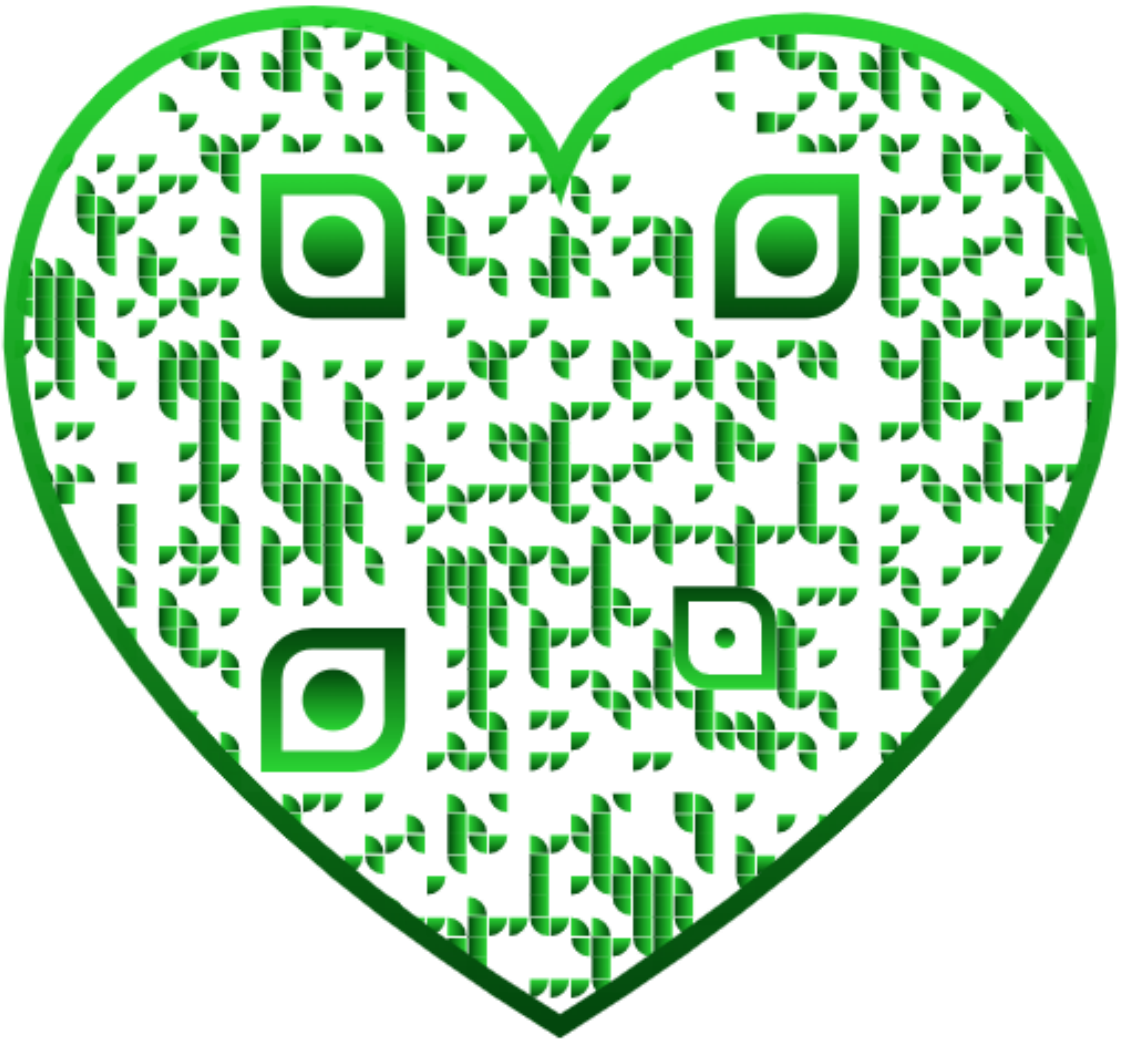
Study Designs in Pharmacoepidemiology

Sisay E.



Sources of Knowledge

- Two major approaches of knowing the world:
  1. **Everyday experience and**
  2. **Science**
- **1. Everyday Experience as Sources of Knowledge**
  - **The Method of Tenacity**
    - Acceptance of a belief based on the idea that "***we have always known it to be this way"***
    - Automatic acceptance of the prevailing traditional beliefs and customs in which we have been socialized

Sources of Knowledge…

- **Two problems of Tenacity**
  - The information may gain wide acceptance through its familiarity alone
  - Tenacity offers no means for correcting erroneous ideas.
    - *E.g: Is darker colored 'injera' more nutritious?*
- **The Method of Authority**
  - If we are naïve to most of the practices what we do, we ask someone in that culture who is supposed to have the knowledge – an authority figure.
    - E.g *a physician may tell us that smoking affects our health.*

Sources of Knowledge…

- **The Priori Method**
  - First we develop **general** knowledge, opinion, or belief about the world through the aforementioned methods or personal observation of things around us and then we draw **new** and **specific** conclusion from this general knowledge.
  - Known as a **deductive reasoning**
    - ***Example:*** *All men are tall; Alemu is a man; therefore, Alemu is tall.*
    - Logical conclusions may not necessarily lead to correct conclusions.

Sources of Knowledge…

- **Common Sense**
  - Based on our own past experiences and our perceptions of the world
  - The concepts that we have about the world may be seriously misleading
  - May help us deal with the routine aspects of daily life
  - May also form a wall and prevent us from understanding new ideas

Sources of Knowledge…

- **2. Scientific Method as a Source of Knowledge**
  - Science is a body of systematized knowledge
  - In scientific method **ideas** are **evaluated** and **corrected** through dispassionately observing by means of our bodily senses or measuring devices
  - Science and common sense **differ** in terms of:
    - Use of **conceptual** schemes and theoretical structures
    - The notion of **control**
    - The **explanations** of different observed phenomena

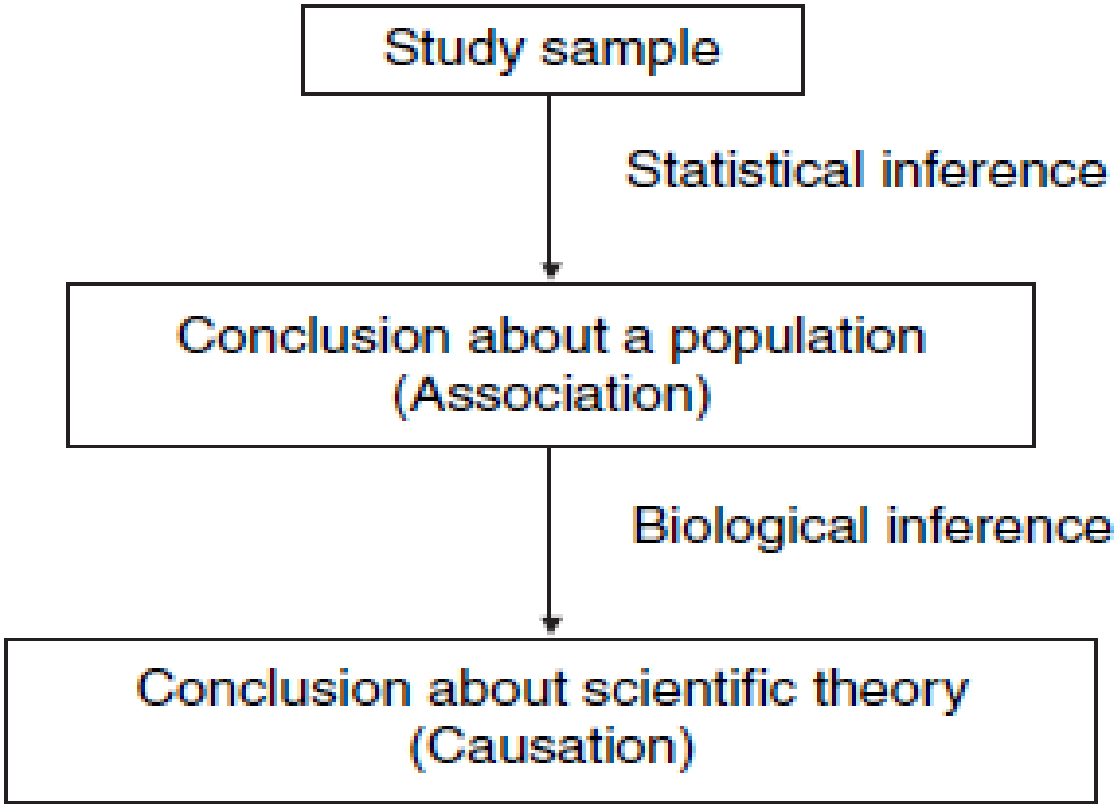
Scientific Method as a Source of Knowledge…

- Scientific research follows logical steps, which include:
  - Defining the problem
  - Making tentative explanations
  - Gathering information
  - Testing the validity of the hypothesis
  - Making conclusions as to whether the hypothesis can be accepted or rejected

Overview of scientific methods

- The scientific method is a **three-stage** process
  - First, **selects** a group of subjects for study (Sample)
  - Second, **Generalize** and draw a conclusion about a **population**
    - This conclusion is referred to as an **association**
  - Third, drawing a conclusion about **scientific theory or causation**

Overview of scientific methods…



Overview of scientific methods…

- **Example**
  - RCT on the efficacy of enalapril in lowering BP by randomly allocating a total of **40 middle-aged hypertensive** men to receive either **enalapril** or **placebo** and observing their BP **six weeks later**
  - **Expected outcome**
    - Enalapril **lower the BP** of the 20 men compared to the BP of the 20 men treated with a **placebo**
  - Study **sample/** subject
    - 40 men → **sample size**
    - **Representative**
      - Middle-aged hypertensive men (target population)

Overview of scientific methods…

- Conclusion about population or **association**
  - Enalapril lowers BP in middle-aged hypertensive men
- Conclusion about scientific theory or causation
  - Enalapril is an antihypertensive drug in general
- To generalize **Enalapril** lowers BP in middle-aged hypertensive men
  - Rule out the association is not b/c of **chance, bias, confounder and then apply the criteria for the causal nature**

Overview of scientific methods…

- Epidemiological studies aim to provide accurate measures of health related event or states
  - **Error in measurement**
    - Minimize error
    - Assess the impact of error
  - Error → **random + systemic**
- **Random error**
  - When a value of sample measurement diverges from the true population due to chance alone

Overview of scientific methods

- **Chance**
  - **Random error** or variation
  - Sampling error, measurement error, biological variation
  - Perform a statistical test to quantitate the probability that the observed outcome in this study
    - (e.g. enlalpril and placebo taking) **could have happened simply by chance**.
  - "**statistically significant difference**," then one is said to have an *association.*

Overview of scientific methods…

- **Systemic error or bias**
  - Any **systematic error** in the **design**, **conduct** or **analysis** of a study that results in a mistaken estimate of an exposure- effect on the risk of disease/outcome
  - Systematic variation occur **when two study groups** are treated or evaluated **differently**.

Overview of scientific methods…

- **Systemic error or bias…**
  - E.g. **Selection bias → healthy worker effect**
    - In a factory where workers are exposed to **formaldehyde,** those who suffer from eye irritation are most likely to lose their jobs.
    - The remaining workers are less affected and a prevalence study of the association b/n formaldehyde exposure and eye irritation that is done only in the work place may be very misleading.
- **Measurement bias**
  - Specimen from exposed and non exposed (control) are analyzed by different laboratories

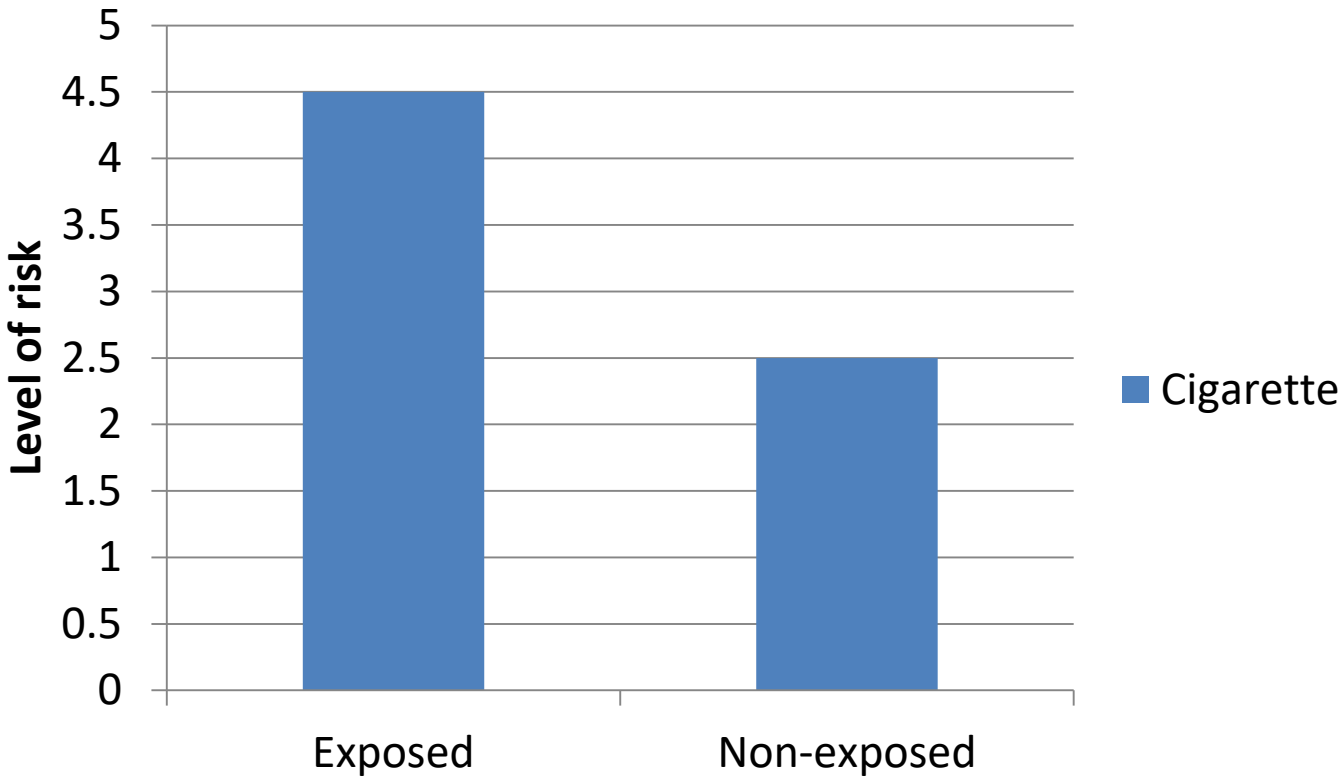
Overview of scientific methods…

- **Recall bias**
  - Differential recall of information by **cases** and **control**
    - E.g Lack of exercise and heart disease
- **Observer bias**
  - If the investigator, lab technician or participant knows the exposure status
  - Knowledge cause influence
- **Bias** create an **apparent** association where one actually does not exist or can **mask** a true association
  - E.g. Selection bias, Information bias**,** Interviewer bias, Recall bias
- ***NB!*** biases once present, cannot be corrected.
  - *a statistically significant result is no protection against a bias*

Overview of scientific methods…

- Association: estimating risk
  - **Absolute risk**: The incidence of a disease/event in a population
  - **Attributable risk (AR)** or **risk difference or excess risk**:
    - Difference between the risk measured in an exposed population (the absolute risk) and that measured in non exposed population
  - **Relative risk** (RR) (RR<1, RR=1, RR>1)

Total risks of cancer in exposed and non-exposed groups



Overview of scientific methods…

- **Odds ratio (OR)**: Ratio of two odds, each being ratio of one probability to its complementary probability (OR<1, OR=1, OR>1)
- **Odds:** The probability that an event will occur divided by the probability that it will not occur
- To draw this type of conclusion
  - Requires one to generalize to populations other than that included in the study, including types of people who were not represented in the study sample, such as women, children, and the elderly

Overview of scientific methods….

- **Biological inference**
  - Examine the data at hand in light of all other relevant data in the rest of the scientific literature
  - Make a **subjective** judgment
  - Use "**Criteria for the causal nature of an association**" or "apply **Doll Hill Guideline**,"

Overview of scientific methods….

- There are four basic types of associations
  - **No** association or independent
  - **Artifactual** association (a spurious or false association)
    - Two mechanisms: Chance and Bias
  - Indirect (**confounded**)
  - Causal (**direct** or true)

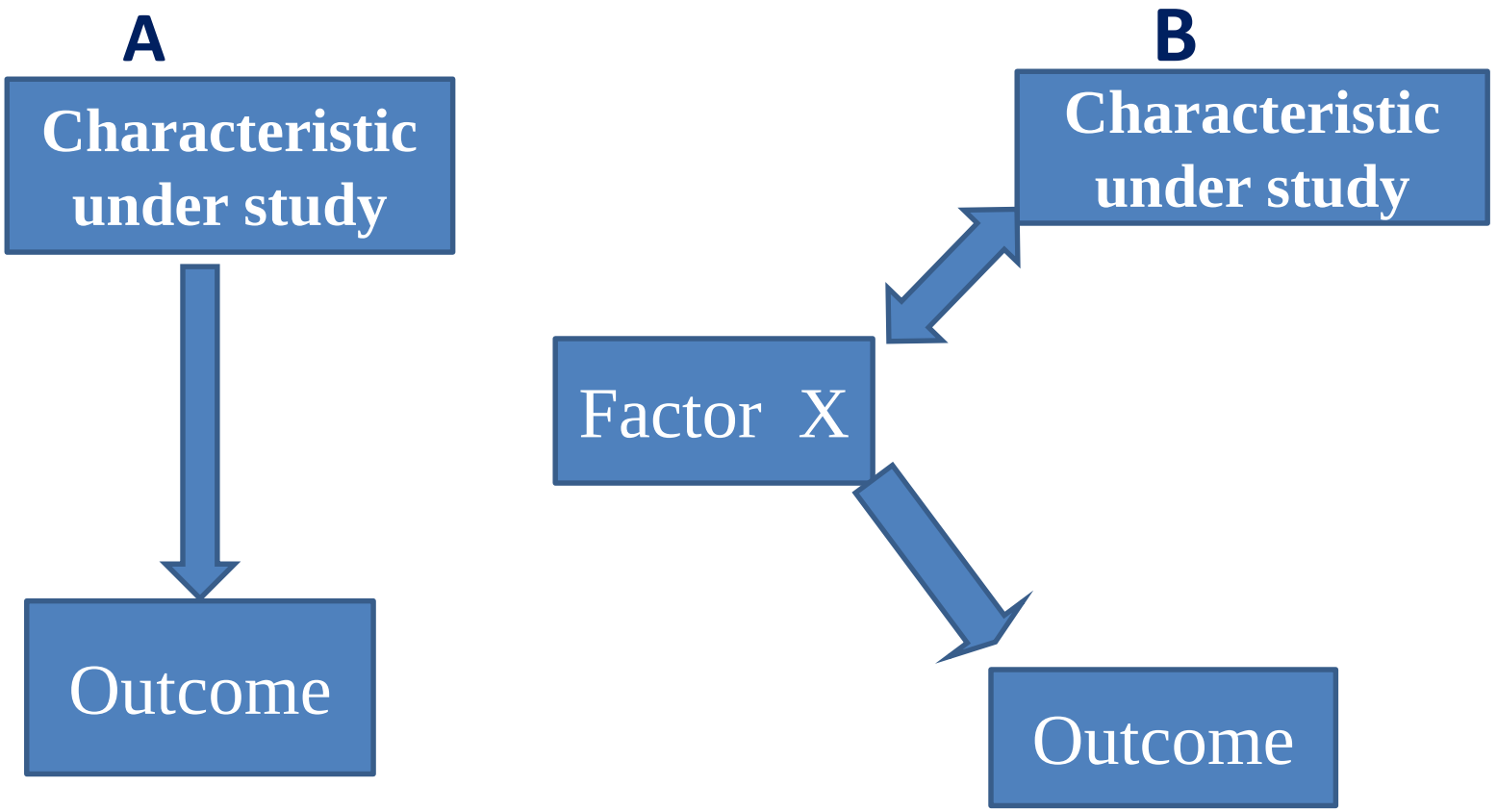
Indirect, or confounded association

- A confounding variable or confounder
  - Is a variable other than the **risk factor** and **outcome** under study
  - Related **independently** to both the risk factor and the outcome variable
  - May create an **apparent** association or **mask** a real one

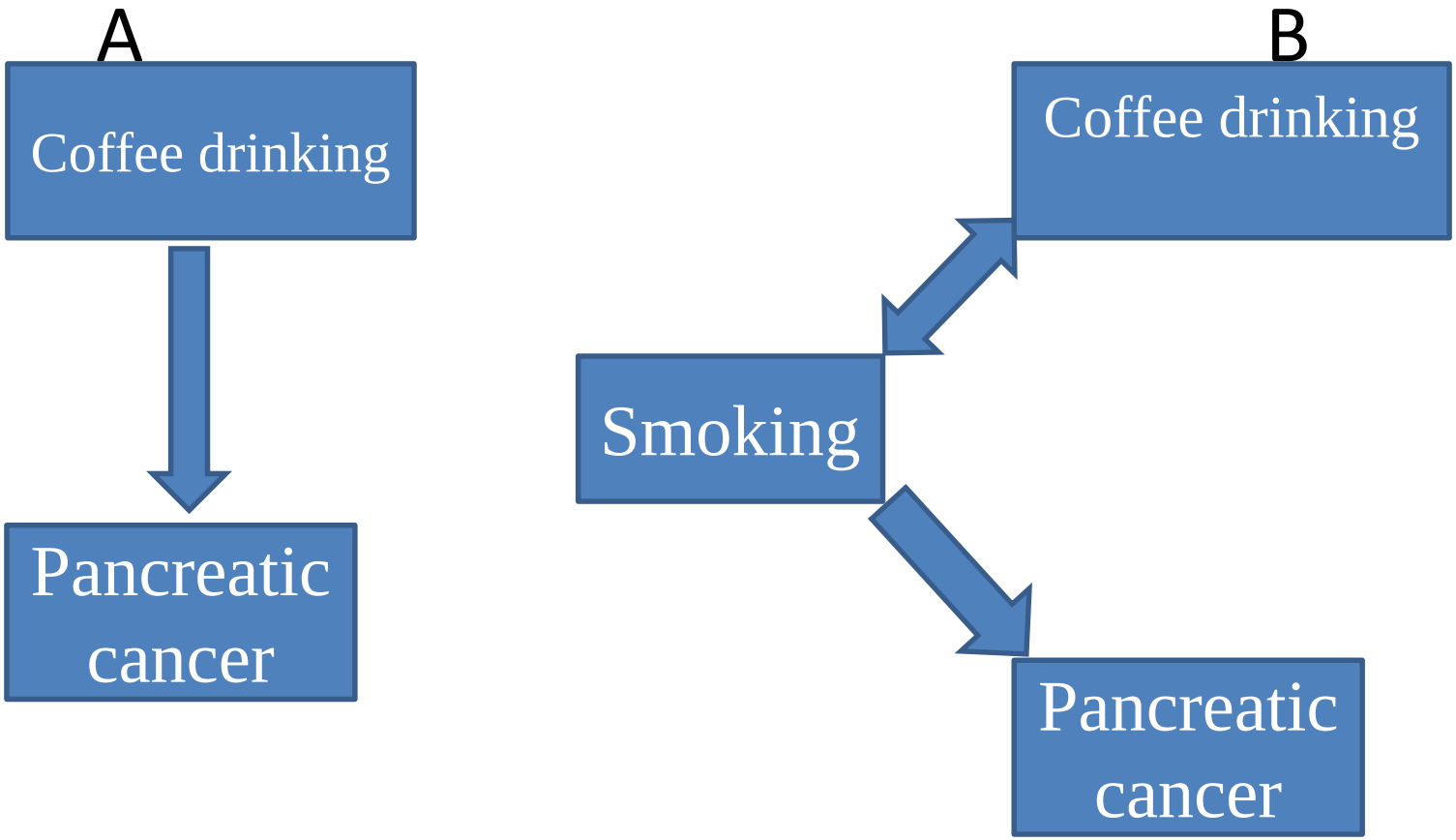
Confounder

- In a study of whether factor **A** is a cause of disease **B**, we say that a third factor, factor **X**, is a confounder if the following are true:
  - 1. Factor X is a **known** risk factor for disease B.
  - 2. Factor X is **associated** with factor A, but is not a result of factor A.
    - E.g 1 McMahon observed an association of **coffee** consumption with risk of **pancreatic cancer**
    - Was the observed association of **coffee** drinking and cancer of the **pancreas** likely to be a **causal** relationship?

A. Causal B. Due to confounding



A. **Causal** **B. Due to confounding**



Confounder…

- Smoking (factor X) was a confounder
  - 1. Smoking is a **known** risk factor for pancreatic cancer (disease B)
  - 2. Smoking is associated with coffee drinking, but is not a result of coffee drinking (factor A)
  - ***NB*** ! coffee drinking and cigarette smoking are closely associated (few smokers do not drink coffee)

Confounder…

- **Approaches to control confounding**
  - Random allocation
  - Subject selection
    - Exclusion
    - Matching (case vs control)
- Data analysis
  - Stratification
  - Mathematical modeling

Criteria for the causal nature of an association or "Doll Hill guideline"

- No one of them is absolutely **necessary/ sufficient**
  - For a **causal** association
- The more criteria that are present, the more likely to be a causal association

I. Coherence with existing information or biologic knowledge (biological plausibility)

- Data from other human studies
- Data from animal studies
- Data from *in vitro studies*
- Scientific or pathophysiologic theory

Criteria for the causal nature…

- **Example:**
  - **Cigarettes** could cause lung cancer lung cancer
    - In **animal** data → cigarette smoking is a known carcinogen
    - In **humans**, it is known to cause cancers of the head and neck, the pancreas, and the bladder.
    - ***Thus, it certainly is biologically plausible that cigarettes could cause lung cancer***

Criteria for the causal nature…

II. Consistency of the association or replication of the findings

- Science is reproducibility
  - Different geographic **settings**, study **designs**,
  - Different **populations**, etc.

- **Example**
  - The case of cigarettes and lung cancer,
- One should never believe a finding reported only **once**
  - **Error** committed in the study

Criteria for the causal nature…

III. Time sequence (temporal relationship)

- A cause must precede an effect
- Ex. Cigarette smoking precedes the lung cancer

IV. Strength of the association

- Quantitative strength
- Study design

Criteria for the causal nature…

V. Dose-response relationship

- As the dose of exposure increases, the risk of disease also increases.
- **Absence** of a dose-response relationship does not necessarily **rule out** a causal relationship
- In some cases in which a threshold may exist,
  - No disease may develop up to a certain level of exposure (a threshold)

Criteria for the causal nature…

V. Specificity of the association

- When a certain **exposure** is associated with only one disease
- **Weakest** of all guidelines

VI. Cessation of Exposure

- If a factor is a cause of a disease, we would expect the risk of the disease to **decline** when **exposure** to the factor is **reduced** or eliminated.

Types of causal relationship

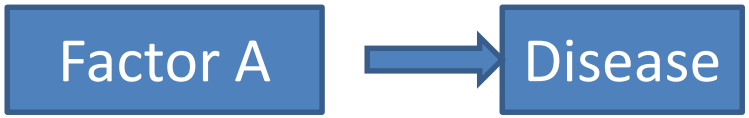
- A causal pathway can be either ***direct*** or ***indirect***
- ***Direct*** **causation**
  - A Factor directly causes a disease without any intermediate step
  - **Factor →Disease**
- **In *indirect* causation**
  - A factor causes a disease, but only through an **intermediate** step or steps.
  - **Factor** →Step 1 → Step 2→**Disease**

Types of causal relationship…

- In human biology, **intermediate** steps are virtually always present in any causal process.
- There are **four** types of possible causal relationships
  - Necessary and sufficient
  - Necessary, but not sufficient
  - Sufficient, but not necessary
  - Neither sufficient nor necessary

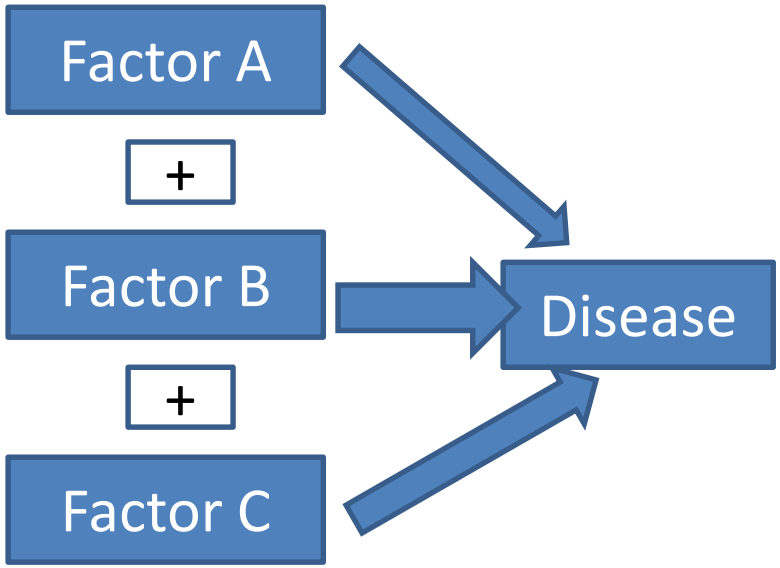
Types of causal relationship…

- **Necessary and sufficient**
  - a **factor** is both necessary and sufficient for producing the disease.
  - Without that factor, the disease never develops (the factor is necessary)
  - in the presence of that factor, the disease always develops (the factor is sufficient)
  - This situation rarely if ever occurs



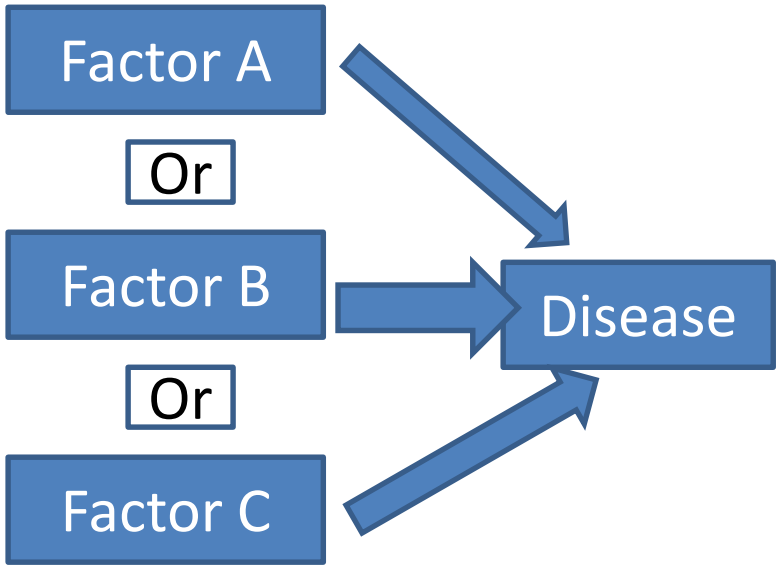
Types of causal relationship….

- **Necessary, But Not Sufficient**
  - Each factor is necessary, but not, in itself, sufficient to cause the disease
  - E.g. in **tuberculosis**, the ***tubercle bacillus*** is clearly a necessary factor, even though its presence may not be sufficient to produce the disease in every infected individual.



Types of causal relationship…

- **Sufficient But Not Necessary**
  - the **factor alone** can produce the disease, but so can other factors that are acting alone
  - E.g. either **radiation** exposure or **benzene** exposure can each produce **leukemia** without the presence of the other.

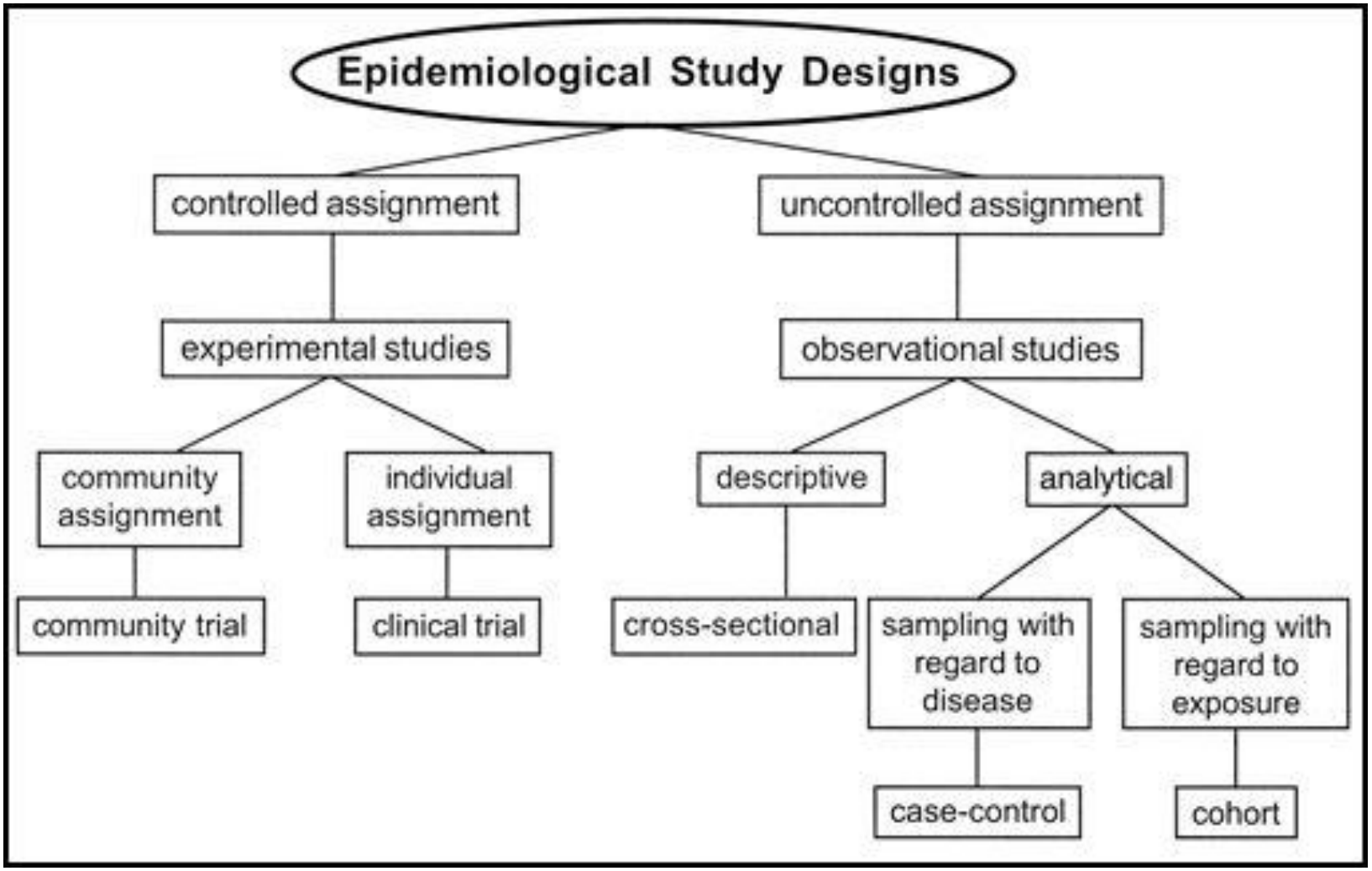


Common Pharmacoepidemilogic Study Designs

Study Designs

- **A study design**
  - It is a specific **plan** or **protocol** for conducting the study, which allows the investigator to translate the **conceptual hypothesis** into an **operational** one.
  - An approach for systematically collecting, analyzing, and interpreting data
    - It is a formal approach of scientific investigation

Types of study designs



Types of study designs…

- Qualitative Vs Quantitative
- Quantitative
  - **Experimental**
    - Studies that entail manipulation of the study factor (exposure) and randomization of subjects to treatment (exposure) groups
  - **Observational**
    - Studies that do not involve any intervention or experiment

Types of study designs…

- Studies can be designed to be **retrospective** or **prospective**.
  - **Retrospective** : data were collected and recorded previously
  - **Prospective** : the collection of data is planned in advance and actually occurs after the study has begun

Comparison of Retrospective and Prospective Approaches

Retrospective

- **Inexpensive** to conduct
- Completed in a **shorter time** period
- **Easier** to access a **larger** number of subjects
- Allows **results** to be obtained more quickly
- Useful for studying **exposures** that **no longer occur**
- Data **less** complete and inaccurate
- Subjects may not remember past information

Prospective

- **Expensive** to conduct
- Completed **over** a longer **time** period
- More **difficult** to access **subjects** and usually requires a **larger** number of subjects
- **Exposure** status and **diagnostic** methods for disease may change
- Loss of subjects from the study over time may be substantial
- **Data** more **complete** and accurate
- Direct access to study subjects enhances **reliability** of **data**

Observational studies: Descriptive studies and Analytical studies

- **Observational**
  - studies that **do not** involve **any intervention** or experiment.
  - involves observation of the disease, drug use problem, or other phenomenon of interest
    - E.g case reports, Case Series, cross-sectional studies, case-control studies, and cohort studies
- **Observational Design**
  - Descriptive epidemiology
  - Analytic epidemiology

Observational studies: Descriptive studies and Analytical studies…

- **Descriptive epidemiology**
  - Concerned with describing the general characteristics of the distribution of disease/pheneomena, particularly in relation to person, place, and time.
  - *What, Who, When, and Where of health-related events*
- **Analytic epidemiology**
  - The process of **testing** a specific **hypothesis** about a potential **exposure** and an **outcome** of interest.
  - *Why and How of such*

Case Reports

- **Case reports**
  - A detailed description of the experience of a single patient.
  - Are simply **reports** of events observed in **single patients**.
  - Useful for **generating hypotheses**
    - **E.G** about drug effects
  - **A young woman who was taking oral contraceptives and who suffered a pulmonary embolism.**
  - The most common type of study published in the medical literature.

CASE REPORTS…

- **Case reports…**
  - Very rarely used to make a statement about **causation** **except**
  - *When the outcome is **so rare** and so **characteristic** of the exposure*
    - Example: **clear cell vaginal adenocarcinoma occurring in young women exposed *in utero to diethylstilbestrol***
  - *When the **disease course** is very **predictable** and the **treatment** causes a clearly apparent change in this disease course*
    - **Example:** The ability of **penicillin** to cure streptococcal **endocarditis**, a disease that is nearly uniformly **fatal** in the absence of treatment.

CASE REPORTS…

- Challenge: re-challenge data to help establish causality (challenge-administarion of the drug)
    - **Example:** a patient who is suffering from an **overdose** of **methadone** and is **comatose**.
        - If this patient is then treated with naloxone and immediately awakens
        - As the naloxone wears off the patient would become comatose again

CASE SERIES

- Case series
  - Describes the characteristics of a **number** of patients with a given disease, characteristic, or exposure.
  - Are collections of patients, all of whom have a single exposure, whose clinical outcomes are then evaluated and described.
  - Collections of patients with a single outcome, looking at their antecedent exposures.
- **Example**
  - **One might observe 100 consecutive women under the age of 50 who suffer from a pulmonary embolism, and note that 30 of them had been taking oral contraceptives.**

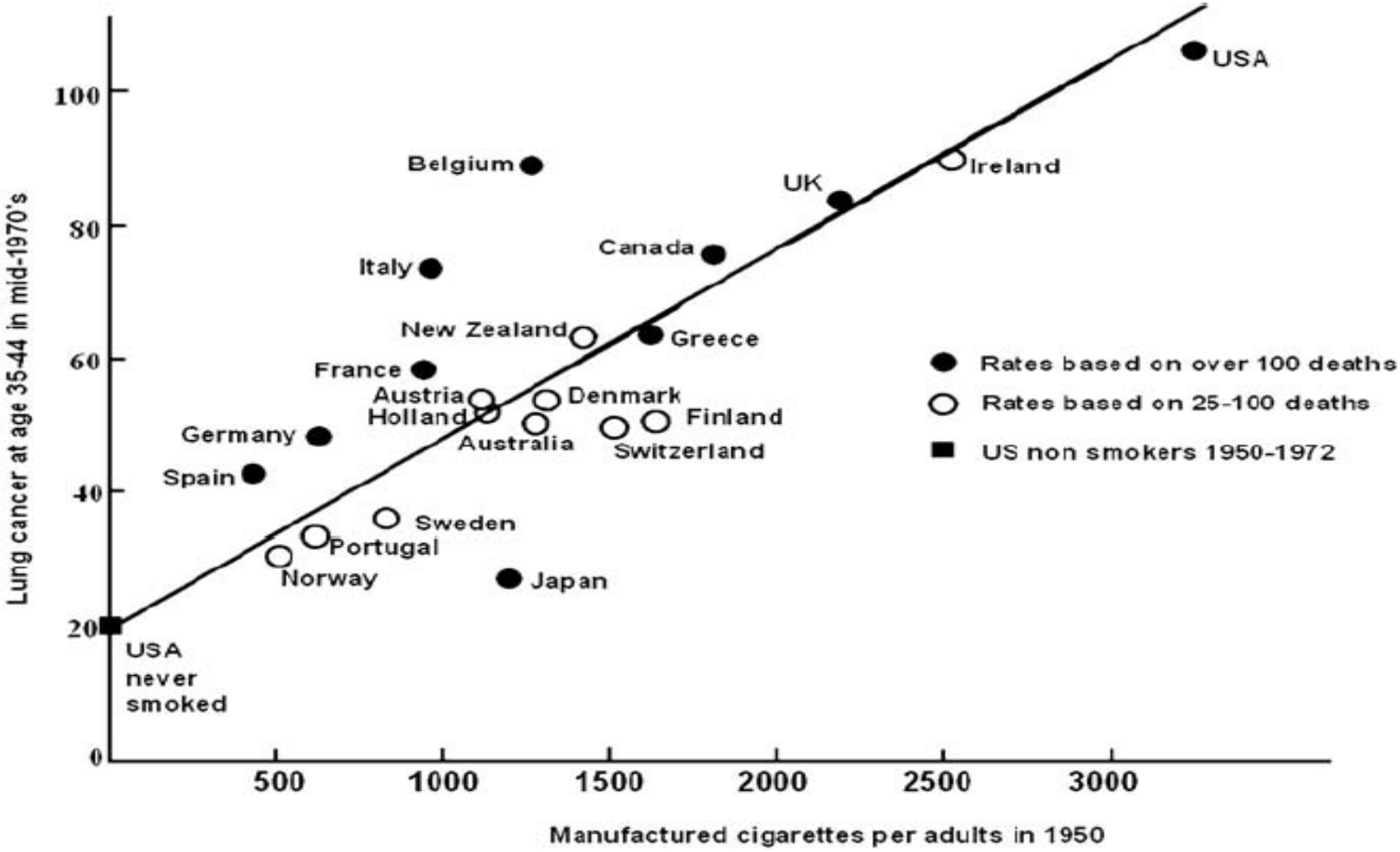
CASE SERIES…

- **After drug marketing**, case series are most useful for two related purposes.
  - **Quantifying** the incidence of an ADR
  - Reassure about the occurrence of any ADR
- **Limitations of case reports and case series**
  - Case reports are based on the **experience of only one person**; that is, the information is **anecdotal**.
  - Case series lack an appropriate **comparison** group.

Ecological Studies

- **Ecological** or **correlational** studies
  - use data from **entire** populations to compare outcome (disease) frequencies either between **different** groups during the **same period of time** or in the **same population** at different points in **time**.
  - Use preexisting sources of information collected for other purpose
  - useful for ***generating hypothesis***
  - The unit of analysis is ***group of people*** rather than individuals
  - Information is collected not on individuals but on groups of people..
  - Example schools, towns, countries, race, religion, or socio-economic status etc.

International correlation between manufactured cigarette consumption per adult in 1950 and lung cancer rates in that generation as it enters middle age (in the mid-1970s).



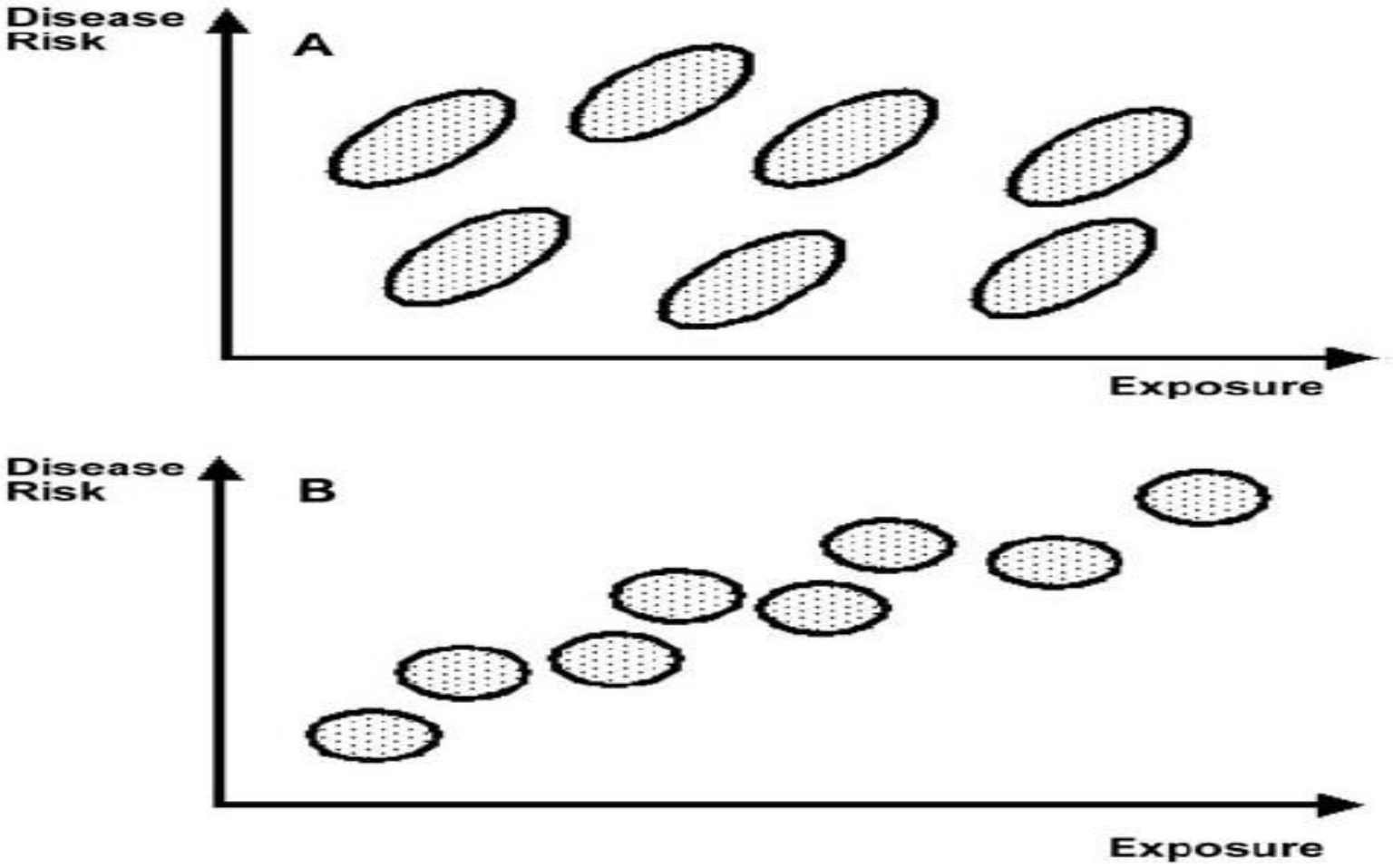
Ecological Studies…

- **Example**
  - sales data for **oral contraceptives** and compared to death rates from venous thromboembolism (**VT**), using recorded vital statistics.
  - Mortality rates from VT were seen to increase in parallel with increasing oral contraceptive sales, but only in women of reproductive age, not in older women or in men of any age.
- *Ecological* studies or analyses of secular trends
  - Are **simple to conduct**
  - Useful for rapidly providing **evidence for** or **against** a hypothesis.
  - But **lack** data on individuals
  - The link b/n **exposure** and **effect** at ***individual*** level can not be made since the unit of analysis is a group
  - **Unable** to control for **confounding** variables

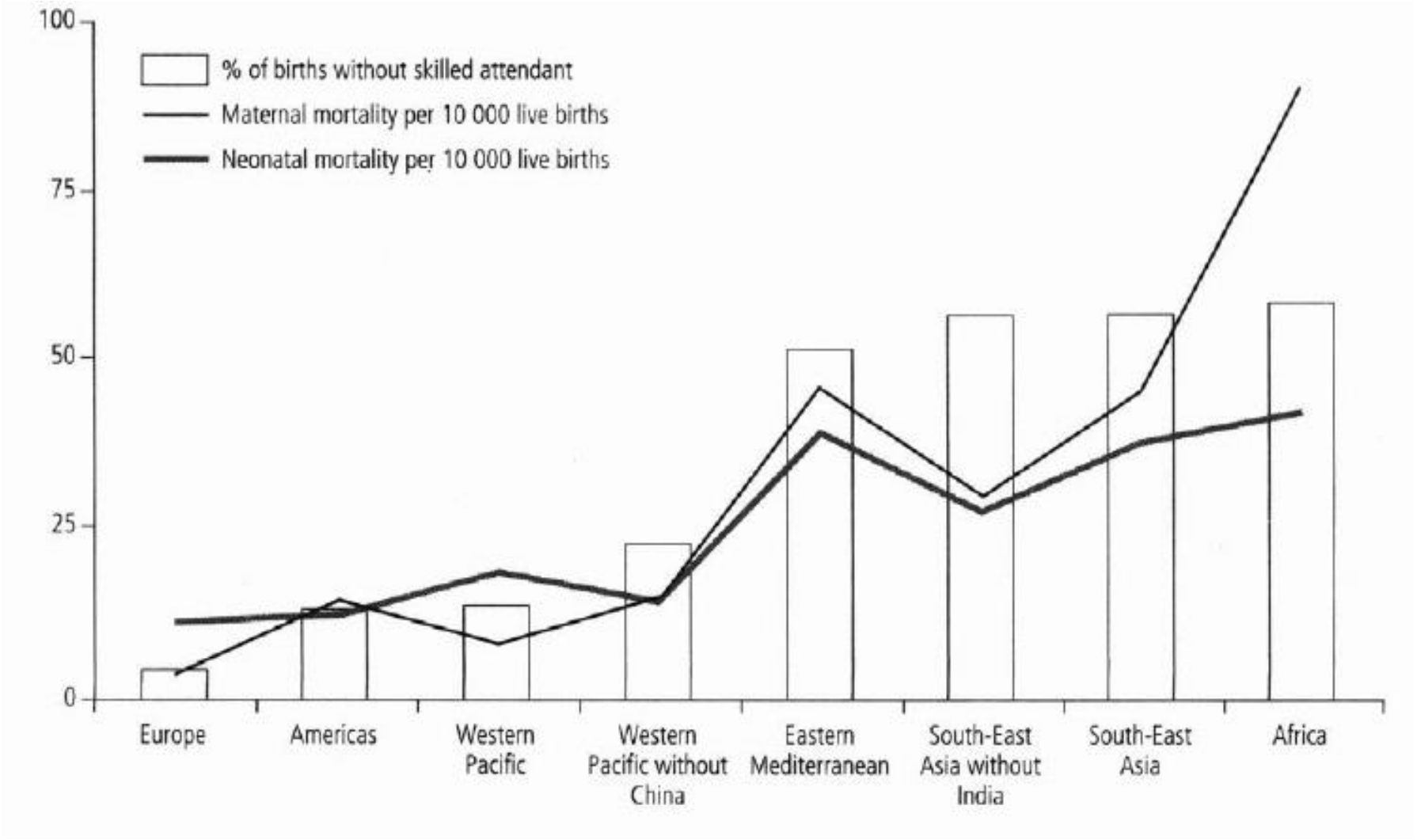
Ecological Studies…

- ***Ecological fallacy or bias***
  - Results if inappropriate conclusion are drawn on the basis ecological data
  - The bias occur b/c the **association** observed at the **group** level does not necessarily represent the association that exist at individual level
  - Unable to differentiate **which** factor is likely to be the **true** cause among exposures whose trends coincide with that of the disease,
  - Example, **lung** cancer mortality rates in the US have been increasing in **women**
  - **Consistent** with
    - increasing rates of **cigarette** smoking observed in women until the mid-1960s
    - an **association** between certain **occupational** exposures and lung cancer, as **more** women in the US are now working **outside** the home.

Two situations illustrating the difference b/n ecological and individual associations b/n exposure and disease



Neonatal and maternal mortality are related to the absence of TBA



Cross sectional studies

- A cross-section survey
  - Assesses the status of an individual with respect to the **presence or absence** of both **exposure** and **disease** at the **same point in time**.
  - It provides a **snapshot** of the experience of a population at a specified time
  - are conducted in order to examine the **prevalence** of a particular condition at a certain point in time
  - Also called **prevalence** studies

Cross sectional studies…

- **Advantages**
  - Comparatively **cheap** and **quick**.
  - Fairly ***simple*** *to carry out and* analyze.
  - It provides estimates of **prevalence** of disease or other health outcomes.
  - It can study **entire populations** or a **representative** sample.
  - It provides greater ability to be **generalized**.
  - Useful for healthcare **planning** and investigating **trends** over time.
  - Useful when **routine** data are not available

Cross sectional studies…

- **Disadvantages**
  - Since exposure and disease are assessed at the same time, the **temporal relationship** between an exposure and disease cannot be determined.
  - It is subject to selection and observation **bias**
  - Sampling and data collection need great care
  - Not useful for conditions which have a **short duration**
  - Not the first choice for investigating **causality**

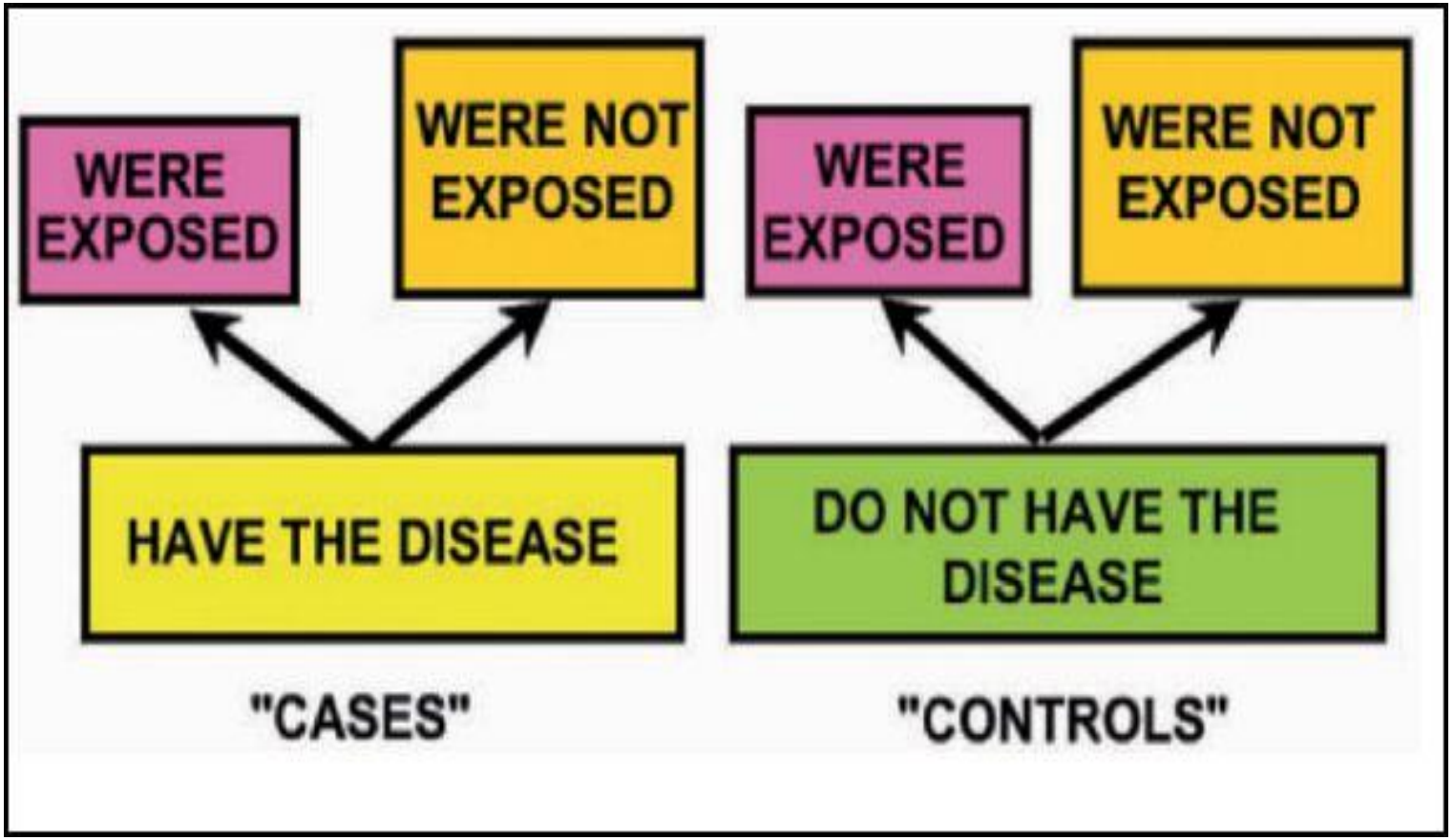
CASE-CONTROL STUDIES

- **Case–control studies**
  - *are studies that compare **cases** **with** a* disease to **controls** **without** the disease, looking for differences in antecedent **exposures**
  - **Cases**
    - people who have developed the disease or outcome in question.
  - **Controls**
    - people who do not have the disease or outcome in question
  - Done to identify factors that could be **responsible** for the development of a **disease** or **drug use problem**.

CASE–CONTROL STUDIES . . .

- **Example**
  - selecting **cases** of young **women with VT** and compare them to **controls without VT**, looking for differences in antecedent ***oral contraceptive use***.
  - Looking for association between the use of oral contraceptives & VT

Design of case control study



CASE–CONTROL STUDIES

Then Measure Past Exposure	***First Select***	
	Cases (With Disease)	Controls (Without Disease)
Were exposed	a	b
Were not exposed	c	d
Total	a + c	b + d

CASE–CONTROL STUDIES…

- a= cases who were exposed, c= cases who were not exposed
- b= controls who were exposed d= controls who were not exposed.
- a + c= total number of cases b + d= the total number of controls
- If exposure is associated with disease, a/(a+c) > b/(b+d) .
- if there is an association of an exposure with a disease, the prevalence of history of exposure should be higher in persons who have the disease (cases) than in those who do not (controls).

CASE–CONTROL STUDIES…

- **SELECTION OF CASES AND CONTROLS**
- ***Selection of Cases***
  - Need to specify the criteria for defining a person as a case
    - i.e. ***case definition***
      - *eligibility criteria*
      - exclusion criteria
  - Incident or Prevalent Cases

CASE–CONTROL STUDIES…

- **Incident** cases of a disease (newly diagnosed cases)
  - Problem→ waiting for new cases to be diagnosed
  - Preferable in case-control studies of ***disease etiology***
    - B/c any risk factors we may identify in a study using prevalent cases may be related more to ***survival*** with the disease than to the development of the disease ***(incidence)***.
    - Example, if most people who develop the disease x die soon after diagnosis,
- Prevalent cases of the disease (people who may have had the disease for some time).
    - A larger number of cases is available for study.

CASE-CONTROL STUDIES

- **Selection of Controls**
  - The way the controls are selected
    - A major determinant on the validity of our conclusion.
  - Select controls from the same underlying population as the Cases

CASE–CONTROL STUDIES…

- **Sources of Controls**
  - Non hospitalized Persons as Controls
    - Community, school rosters
    - Selective service lists, and insurance company lists
    - Neighborhood controls
    - Best friend control
    - Spouse
    - Sibling control may be useful
      - a sibling may provide some control over genetic differences between cases and controls.

CASE–CONTROL STUDIES….

- Hospitalized Patients as Controls
    - Hospital inpatients
        - Easy, clearly identified, more economical
        - However, represent a sample of an ill-defined reference population that generally cannot be characterized.
        - Moreover, hospital patients differ from people in the community.
- Case–control studies generally obtain information on exposures **retrospectively**
    - Abstracting medical or employee records
    - Administering questionnaires
    - Interviews
    - Results of chemical or biologic assays of blood, urine, or tissues

CASE-CONTROL STUDIES…

- **MATCHING**
  - Defined as the process of selecting the **controls** so that they are **similar** to the **cases** in certain characteristics, such as **age**, **race**, **sex**, socioeconomic status, and occupation.
  - Two types:
    - 1- Group matching
    - 2- Individual matching.
- Group matching (or frequency matching)
  - E.g. if 25% of the **cases** are **married**, the controls will be selected so that 25% of that group is also married.

CASE–CONTROL STUDIES…

- Individual matching
  - Often used in studies that use **hospital controls**
    - More practical than conceptual
    - E.g. Assume sex and age are considered important variables, and it is thought to be important that the cases and the controls be comparable in terms of these two characteristics.
- Problems with matching
  - *Practical Problems with Matching*
    - Matching to too many characteristics → difficult or impossible to identify an appropriate control.

CASE–CONTROL STUDIES…

- *Conceptual Problems with Matching*
  - Once we have **matched** controls to cases according to a **given characteristic**, we cannot study that characteristic.
    - have artificially established an **identical proportion** in cases and controls
- **USE OF MULTIPLE CONTROLS**
  - 1 *controls of the same type*
  - 2 *controls of different types* E.g. **hospital** and **neighborhood** controls, or controls with different diseases
- Controls of the Same Type
- One case to multiple control **(1:2, 3 or 4)**
  - are used to increase the **power** of the study.
  - a noticeable increase in power is gained only up to a ratio of about 1 case to 4 controls.

CASE–CONTROL STUDIES…

- **Advantage of Case control studies**
  - **Efficient** and **feasible** means to study disease
    - **fewer** subjects or **smaller** sample size requirements
    - **prior** data collection
  - To study **multiple possible causes or risk factor** for a **single** disease
  - To study **chronic** diseases with long **latency periods**.
  - To study relatively **rare disease**
  - provide or suggest **evidence** of an association that warrants public health intervention to reduce exposure to the risk factor

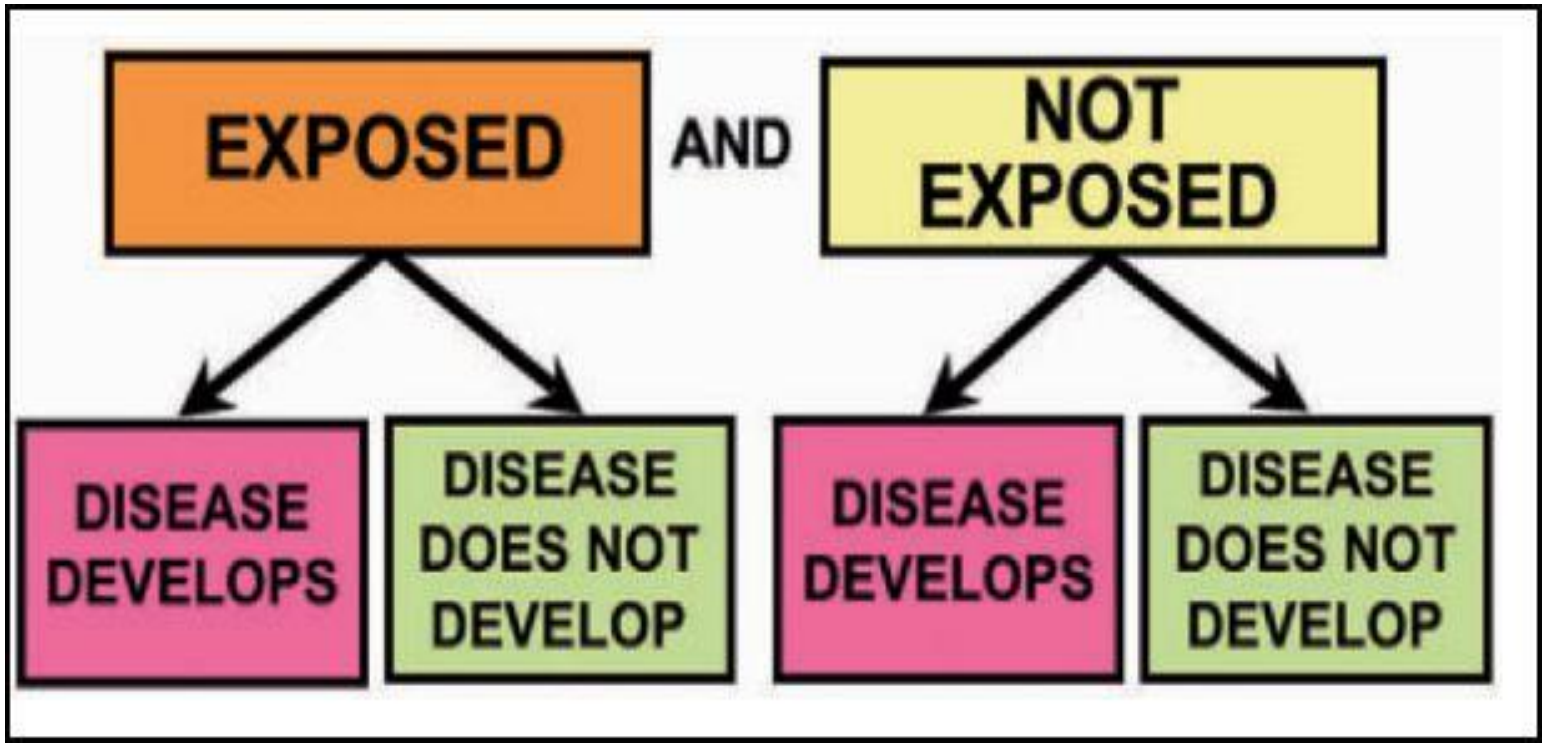
CASE–CONTROL STUDIES…

- **Disadvantages of case-control design**
  - **Cases** and **controls** are **not representative** of the whole population
  - There is **no** direct measure of **incidence** or **prevalence**
  - It is inefficient in situations where **exposure is rare**
  - **Recall bias**
  - **Validity** of retrospectively collected exposure information
  - **Example**
    - The classic study of diethylstilbestrol and clear cell vaginal adenocarcinoma required only **8 cases** and **40 control**s, rather than the many thousands of exposed subjects that would have been required for a cohort study of this question.

COHORT STUDIES

- **Cohort studies**
  - Studies that identify subsets of a **defined** population and **follow** them over time, looking for differences in their **outcome**.
  - Compare **exposed** patients to **unexposed** patients
  - **Example**
    - c**omparing** women of reproductive age who use **oral contraceptives** to users of other contraceptive methods, looking for the differences in the frequency of **VT**.
    - Performed either **prospectively** **or** **retrospectively**

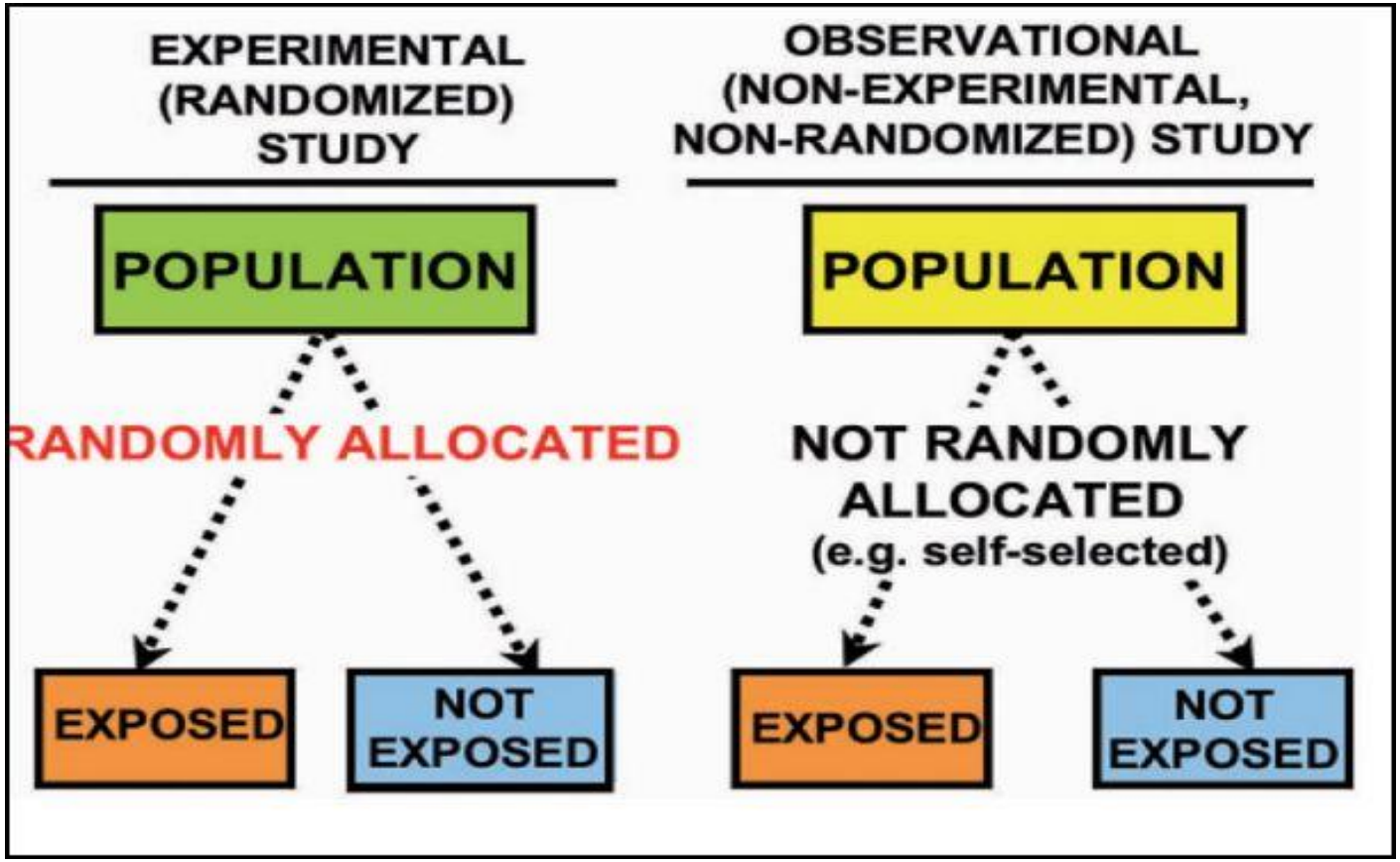
Cohort study design…



COHORT STUDIES…

- Comparing **cohort** and **case–control** studies
  - The difference is the **basis** of **patients selection**
  - *Case–control studies*
    - based on the presence or absence of a **disease**,
    - antecedent **exposures** are then studied.
  - *Cohort studies*
    - the presence or absence of an **exposure**
    - subsequent **disease** course is then studied
- Comparing **Cohort** Studies with **RCTs**
  - Both studies compare **exposed** with **non exposed** groups
  - The difference—the presence or absence of **randomization**

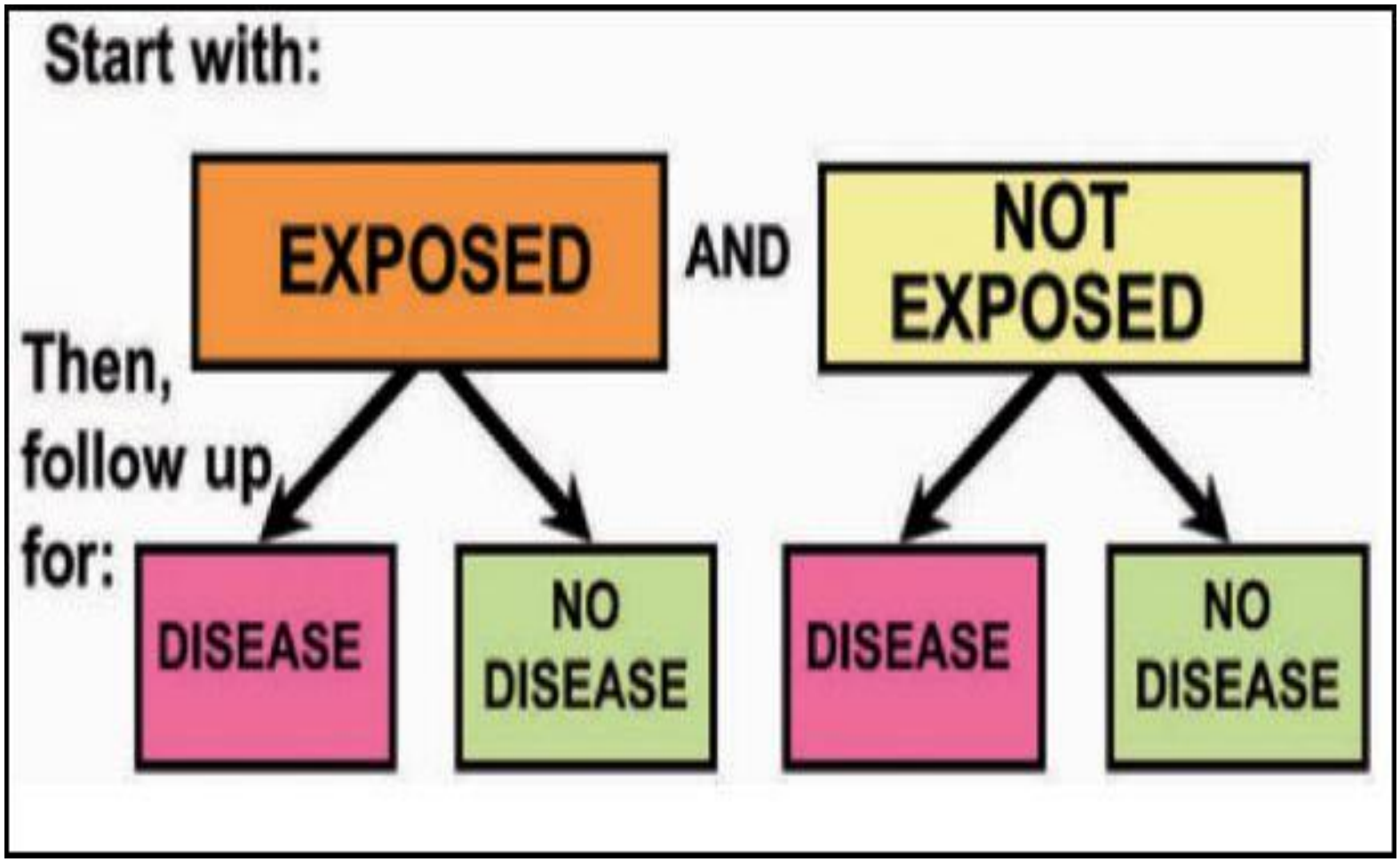
COHORT vs RCT



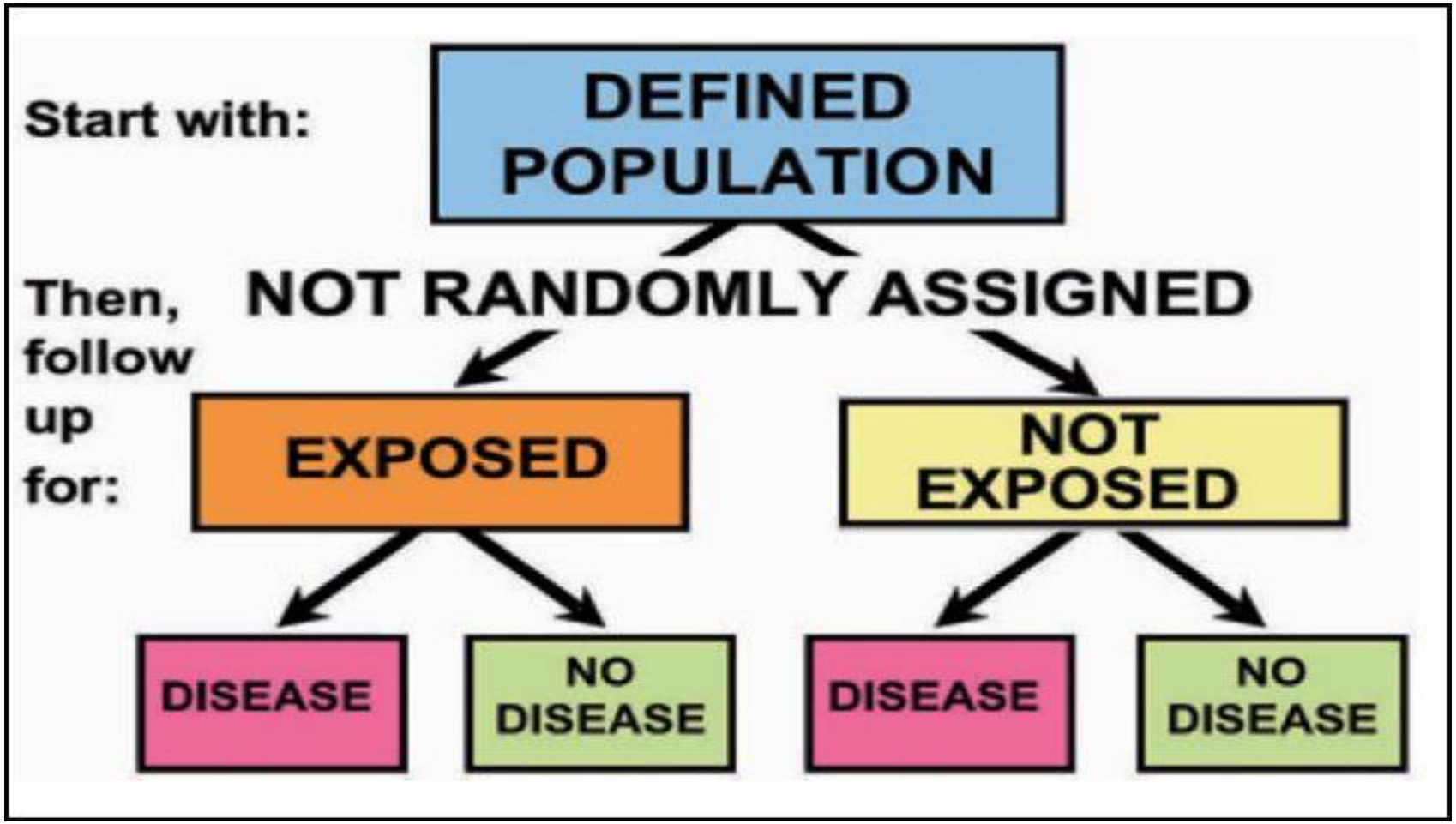
COHORT STUDIES…

- **SELECTION OF STUDY POPULATIONS**
- Two basic ways to generate Exposed and Non exposed group of the study population
  - 1. selecting groups on the their **exposure** status
    - Selecting **already** exposed and non exposed (e.g., occupationally exposed cohorts)
  - 2. selecting a **defined population** before any of its members become exposed or **before** their exposures are identified.

COHORT STUDIES…



COHORT STUDIES…



COHORT STUDIES…

- **TYPES OF COHORT STUDIES**
  - **1. Prospective cohort study**
    - Also called a *concurrent cohort* or *longitudinal study*
    - Exposure and non exposure are ascertained as they occur during the study
    - The groups are then **followed** up for several years into the **future** and **incidence** is measured.
    - Time consuming
    - Difficult to find grant (max 3-5 yrs)
    - Lost to follow up
    - Investigator may not survive to the end of study

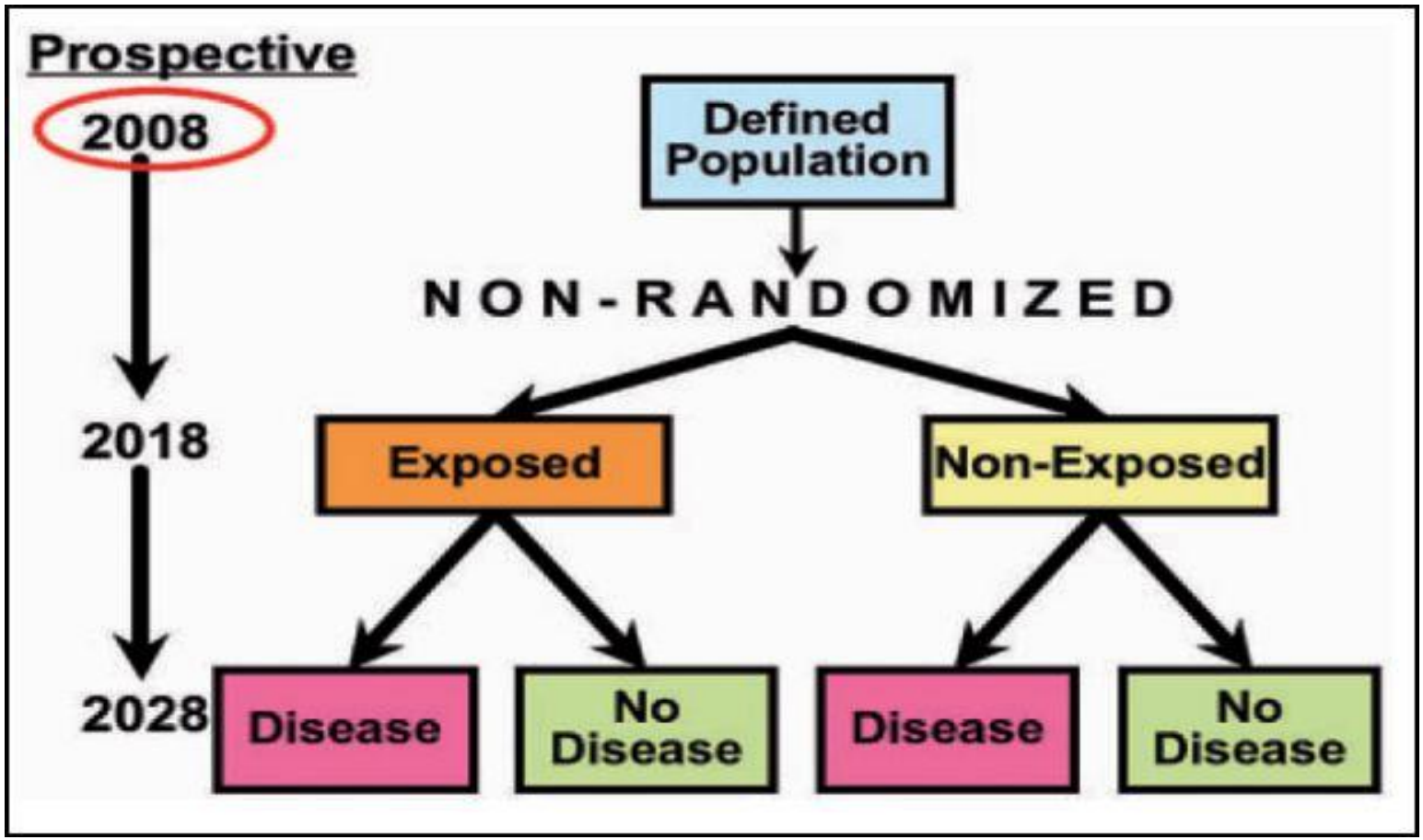
COHORT STUDIES….

- Example: hypothetical study of the relationship of **smoking** to **lung** cancer.
  - Identify a population of **elementary** school students
  - Follow up
  - When they are **teenagers**, we identify those who are smoker and non smoker 10 years later.
  - Then follow up both groups—smokers and nonsmokers—to see who develops lung cancer and who does not.
  - For purposes of this example, let us assume that the **latent period** from beginning smoking to development of lung cancer is 10 years.

COHORT STUDIES…

- Let us say that we begin our study in 2008
  - Because the interval from the time of identification of the elementary school children to the time of identification of their **smoking status** as teenagers or college students is **10** years
  - Exposure status (smoker or nonsmoker) will not be ascertained until the year **2018**.
  - Development of lung cancer will not be ascertained until 10 years later, in **2028.**

COHORT STUDIES…



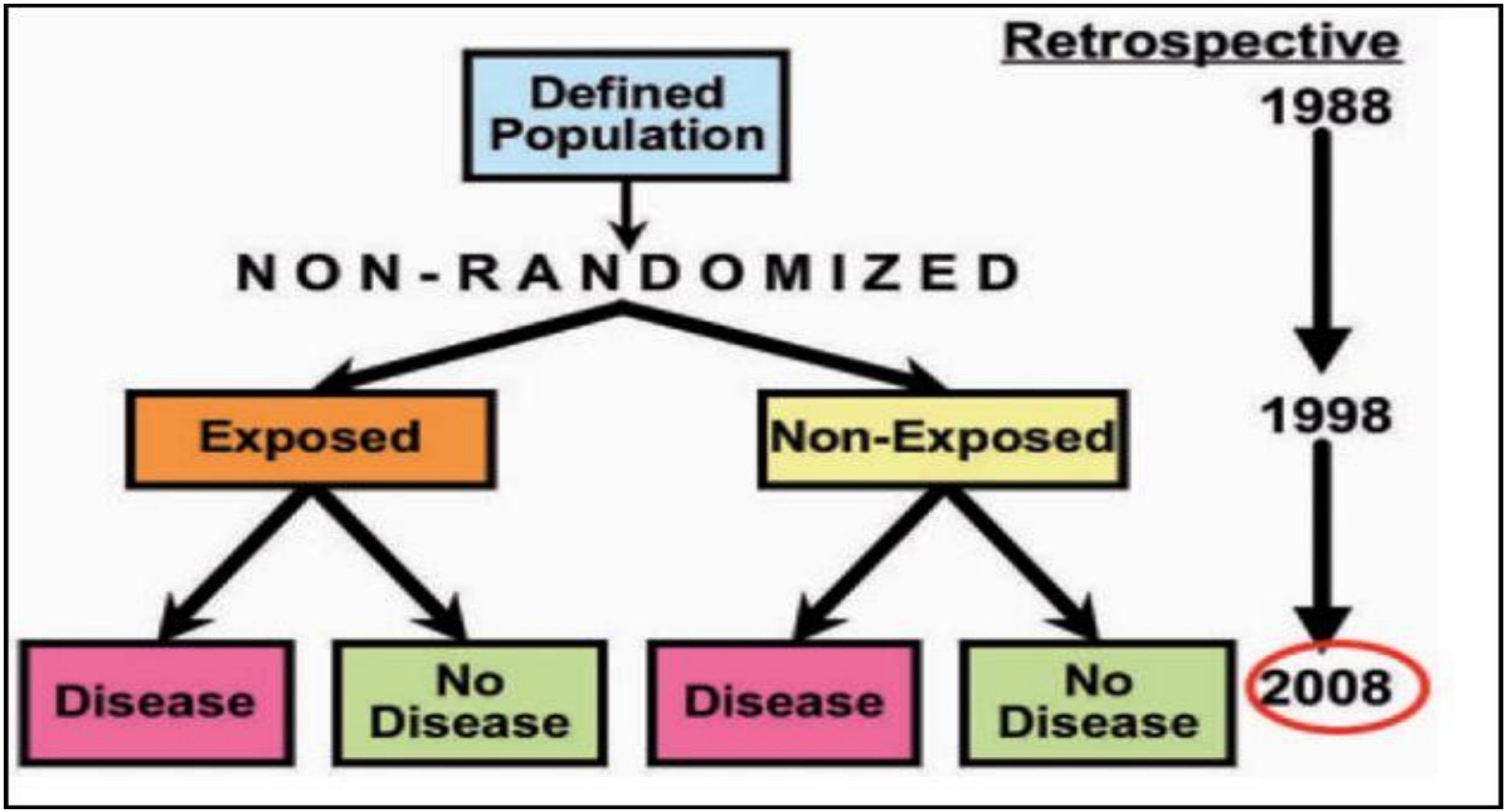
COHORT STUDIES....

2. Retrospective cohort study

- Also called *historical cohort or* a *non-concurrent prospective study*

- Consider the previous example with an alternate cohort design approach .
  - Suppose that we again begin our study in **2008**
  - but now we find that
    - an old **roster** of elementary schoolchildren from **1988** is available in our community
    - they had been surveyed regarding their smoking habits in **1998**
  - Using these data resources in 2008, we can begin to determine who in this population has developed lung cancer and who has not.

COHORT STUDIES…



COHORT STUDIES…

- Retrospective cohort design
  - Use historical data from the past
  - Begin the study with a preexisting population
    - Reduce the duration of the study
  - Difference between **prospective** and **retrospective** cohort
    - Calendar time.
  - NB! In a *retrospective cohort design*,
    - **Exposure** is ascertained from past records
    - **Outcome** (development or no development of disease) is ascertained at the time the study is **begun**.

COHORT STUDIES…

- **Advantages**
  - Allow outcomes to be explored over time.
  - The **incidence** of disease in both exposed and non-exposed groups can be measured.
  - Useful for **rare exposures**.
  - Study **multiple outcomes**
  - More **representative** of the true population than case-control studies **.**

COHORT STUDIES…

- **Disadvantages**
  - Can take a very **long time** to complete or to study delayed drug effects.
  - Diseases with **long latent** periods may need many years of follow-up.
  - Not so useful for **rare diseases** or uncommon outcomes.
    - Require extremely large sample sizes to study relatively uncommon outcomes.
  - Can be very expensive
  - Careful follow-up of all subjects is vital

Analysis of Case-control and Cohort Studies

- **Relative risk (RR)**
  - *is the ratio of the incidence* rate of an outcome in the exposed group to the incidence rate of the outcome in the unexposed group.
  - RR can be calculated directly from the results of a cohort study but not from case control studies
  - RR> 1 means that **exposed** subjects have a ***greater*** risk of the disease under study than **unexposed** subjects, or that the exposure appears to **cause** the disease.
  - RR < 1.0 means that **exposed** subjects have a ***lower*** *risk* of the disease than **unexposed** subjects, or that the exposure seems to **protect** against the disease.
  - RR= 1.0 means that **exposed** subjects and **unexposed** subjects have the same risk of developing the disease, or that the exposure and the disease appear **unrelated**.

- **Case–control study**
  - Do not provide information on the incidence rates of the disease in exposed and unexposed individuals.
  - OR is used in a case-control study
  - *OR* is a close estimate of the relative risk when the disease under study is relatively **rare**.

ANALYSIS OF CASE–CONTROL AND COHORT STUDIES…

- Relative risks and odds ratios
  - reported with p-values and CI
- **P-values**
  - allow to determine if the RR or OR is statistically **significantly different from 1.0**
  - Or whether the **differences** b/n the two study groups are likely to be due to random variation or are likely to represent real associations.
- **Confidence intervals (CI)**
  - are an indication of the range of RR or OR within which the **true** RR or OR for the entire **theoretical population** is most likely to lie.
  - Example , a 95% CI around a RR means that we can be 95% confident that the true RR lies in the range between the lower and upper limits of this interval.
  - ***If a 95% confidence interval around a RR excludes 1.0, then the finding is statistically significant with a p-value of less than 0.05.***

ANALYSIS OF CASE–CONTROL AND COHORT STUDIES`

- A CI provides much more information than a p-value
- example, a study result with
  - RR risk (95% CI) of 1.0 (0.9–1.1)→no association.
    - reported as RR of 1.0 and a p > 0.05.
  - RR (95% CI) of 1.0 (0.1–100) →no association Yet,
    - reported as RR of 1.0 and a p > 0.05.
  - RR (95% CI) of 10.0 (9.8–10.2) precisely quantifies a ten-fold increase in risk that is also statistically significant.
  - RR (95% CI) of 10.0 (1.1–100) is strongly suggestive of an association, a RR of 10.0 p < 005.
  - RR (95% CI) of 3.0 (0.98–5.0) show no association,
    - reported as a RR of 3.0 and p > 0.05.
  - RR (95% CI) of 3.0 (0.1–30) show no association
    - reported as a RR of 3.0 and p > 005.

ANALYSIS OF CASE–CONTROL AND COHORT STUDIES

- *Attributable risk (AR) or Excess risk or risk difference*
  - It is the arithmetic difference between the incidence rates. (I_E-I_{NE})
- **RR** is more important in considering questions of **causation**.`
- **AR** is more important in considering the **public health impact** of an association
  - it represents the increased rate of disease due to the exposure.
- CI and p-value be calculated around excess risks as well, and would be interpreted analogously.
  - to determine whether the differences between the two study groups could have occurred just by chance.
- AR and RR cannot be calculated from case–control studies
  - incidence rates are not available.

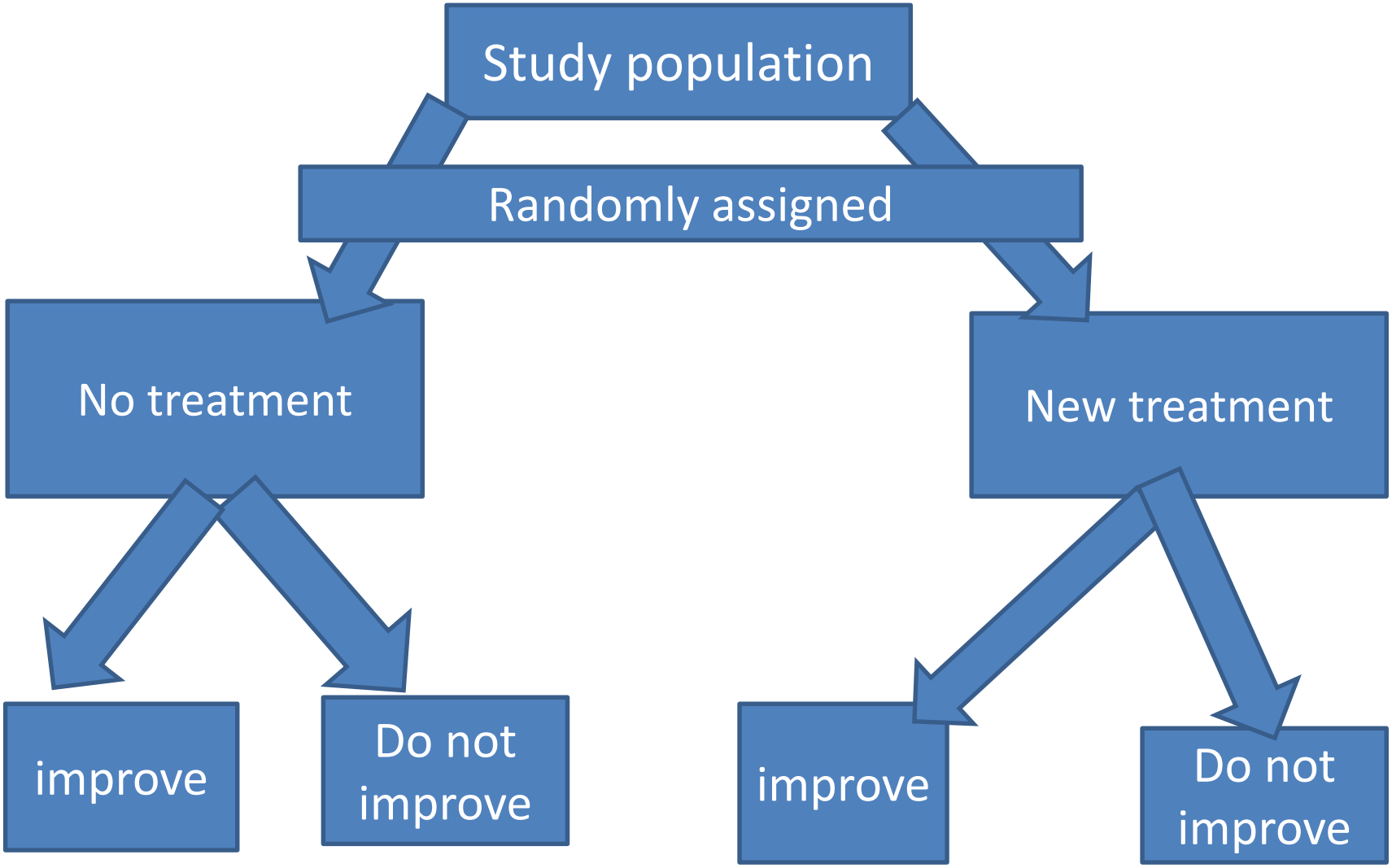
Experimental studies: RCT and Community Intervention Trails (CITs)

- Use of **experimental** design in pharmacoepidemiology
  - Clinical trials, most notably randomized, controlled clinical trials.
    - Involves **people** as the units of analysis.
  - Community intervention study (CITs
    - Involves a **groups of people as** the unit of analysis.
    - **E.g** whole communities
- Randomized trials can be used
  - For **evaluating** new drugs, other treatments of disease, tests of new health and medical care technology.
  - To assess new programs for screening and early detection,
  - To assess new ways of organizing and delivering health services.

RCTs

- *experimental studies are studies in which the investigator* controls the therapy that is to be received by each participant.
- Investigator **randomly** allocate patients between or among the study groups, performing a *randomized clinical trial.*
- **Example**
  - Investigator randomly allocate sexually active women to use either **oral contraceptives** or **no contraceptive**, examining whether they differ in their incidence of subsequent VT.
- Associations demonstrated in RCTs are **more likely to be causal** associations than those demonstrated using observational studies.

RCT


Study population
Randomly assigned
No treatment
New treatment
improve
Do not improve
improve
Do not improve

RCT

A. SELECTION OF SUBJECTS

- The criteria are prepared on who will or will not be included in the study

B. Allocation of Subjects to Treatment Groups

- **Studies without Comparison**
  - Case study, case series
- **Studies with Comparison**
- Historical Controls
  - using a comparison group from the past
  - E.g. comparing **new** treatment with **old** treatment for the **same disease**
  - records of patients with the same disease who were treated before the new therapy became available serve as control
  - simple and attractive

RCT

- **problems in using historical controls?**
  - knowing whether there is a true difference in outcome
    - the observed difference is may be due to a difference in the quality of the data collection
  - knowing whether the difference is a result of the drug being studied
    - b/c changes might taken place in many other factors over calendar time
    - e.g., ancillary supportive therapy, living conditions, nutrition, and lifestyles).
- Simultaneous **Nonrandomized** Controls
  - are not selected in a randomized manner.
    - b/c of the difficulties of dealing with changes over calendar time
  - E.g giving anti-nausea pills for sea **captain** and using the **passengers** as controls."

RCT

- **Goal of randomization**
  - To eliminate possibility of **selection** bias
- Randomization
  - The best approach in the design of a trial
  - Avoid selection bias
    - no subjective biases of the investigators
  - Increase the **probability** comparability of the group
    - E.g sex, age, race, and severity of disease etc
- ***NB : Randomization may not guarantee comparability***
  - ***because of chance***

RCT

- **Stratified** Randomization
  - First, stratify (stratum = layer) the study population by each variable that is considered to be important
  - Then randomize participants into treatment groups within each stratum.
    - E.g, We are studying **1,000** patients and are concerned that **age** and **sex** are important determinants of prognosis.
      - 1st stratify the 1,000 patients by sex into males and females
      - Then stratify the males by age and the females by age

RCT

- The likelihood of the two groups will be comparable in terms of age and sex.
  - E.g. 1000 pts= stratified by sex, then Age
    - 600 males= 360 young + 240 old
    - 400 females= 300 young + 100 old
  - New treatment=180 young male+120 old male+150 young female+50 female=500
  - Current treatment=180 young male+120 old male+150 young female+50 female=500

RCT

C. DATA COLLECTION ON SUBJECTS

- the collected **data** for each of the study groups be has to similar

- Outcome
  - comparable measurements of outcome in all study groups is needed
  - a need for explicitly stated criteria for all outcomes to be measured in a study.
  - Blinding (masking) minimize the problem

RCT

- **Masking (Blinding)**
  - The process of ensuring that almost everyone involved in the drug trial is **unaware** of who is receiving the experimental drug and who is receiving a traditional drug treatment, or a placebo, throughout the duration of the study.
  - **Single-blind**:-
    - Patients lack knowledge about which treatments (experimental or traditional/placebo drug) are receiving
    - when the outcome is a subjective measure e.g headache or back pain.
    - enthusiasm and certain psychological factors may affect the response.

RCT…

- **Double-blind:**
  - Patients and treating clinicians
- **Triple-blind:**
  - patients, treating clinicians, and the scientific investigators

D. CROSSOVER in clinical trials

- Two types: planned or unplanned.
- ***Planned crossover***
  - a **new** treatment is being compared with **current** treatment.
  - Subjects are randomized to new treatment or current treatment
  - After being observed for a certain period of time on one therapy and after any **changes** are measured, the patients are **switched** to the other therapy.

RCT

- **Both** groups are then **again** observed for a certain period of time.
- Changes in Group 1 patients while they are on the **new** treatment can be compared to changes in these patients while they are on **current** treatment.
- Changes in Group 2 patients while they are on the new treatment can also be compared to changes in these patients while they are on current treatment
- **Each patient can serve as his or her own control,** holding constant the variation between individuals in many characteristics that could potentially affect a comparison of the effectiveness of two agents.

RCT

- Caution in using planned cross over
  - ***Carryover:***
    - For example, if a subject is changed from therapy A to therapy B and observed under each therapy, the observations under therapy B will be valid only if there is no residual carryover from therapy A.
    - ***There must be enough of a washout period to be sure none of therapy A, or its effects, remains.***
  - **Order** of treatment may elicit psychological responses.
    - any differences observed are indeed due to the agents being evaluated, and not to any effect of order.
    - Patients may react differently to the first and second therapy
  - Not possible if the new therapy is **surgical** or if the new therapy **cures** the disease.

RCT

Unplanned crossover

- Randomization is carried out after informed consent has been obtained.
  - E.g. surgery vs. medical care (drug tt) for coronary heart disease.
- unplanned crossovers may occur in reality
- Some subjects assigned by the randomization to bypass surgery may begin to have second thoughts and decide not to have the surgery
- They are therefore crossovers into the medical care group and vice versa
- If we want to carry out an intention to treat analysis, we would compare the patients according to their original assignments following randomization.

RCT

E. FACTORIAL DESIGN

- Assuming that **two** drugs are to be tested, the **anticipated outcomes** for the two drugs are different, and their modes of action are **independent**, one can *economically use the same study population for testing both drugs*.

- **Generalizability**
  - internal validity and external validity

RCT

- **ETHICAL CONSIDERATIONS**
  - Is randomization is ethical.
    - **withhold** a drug from patients, particularly those with serious and life-threatening diseases?
    - Randomization is ethical only when we do not know whether drug A is better than drug B.
  - Is it ethical not to randomize?
  - is it ethical to use a placebo?
  - Is that truly informed consent is obtained?

RCT

- REGISTRATION OF CLINICAL TRIALS
  - not all results of clinical trials are published.
  - example, if clinical trials of a new drug are reviewed but only those that show beneficial results have been published and those showing negative results (for some reason) have not been published, an erroneous conclusion that *all* studies of the new drug have shown a clear benefit might be drawn from the published studies.
  - This type of common problem is called ***publication bias*** or non-publication bias.

- Several factors account for the problem of publication bias.
  - **Journals** are more eager to publish results from studies showing dramatic effects
  - **Companies** that develop new drugs and fund studies
    - no benefits, or show serious side effects
    - the drug studied is shown to be less effective than currently available agents.
    - adversely affect sales of the product
- *regulators, physicians, and the public are prevented from making an evidence-based decision*
- All clinical trials of medical interventions must be registered in a public trials registry before any participants are enrolled in the study.

Advantages and disadvantages of epidemiologic study designs

Study Design	Advantages	Disadvantages
Randomized clinical trial (Experimental study)	• Most convincing design • Only design which controls for unknown or unmeasurable confounders	• Most expensive • Artificial • Logistically most difficult •Ethical objections
Cohort study	• Can study multiple outcomes • Can study uncommon exposures • Selection bias less likely • Unbiased exposure data • Incidence data available	• Possibly biased outcome data • More expensive • If done prospectively, may take years to complete

Study Design	Advantages	Disadvantages
Case–control study	• Can study multiple exposures •Can study uncommon Diseases •Logistically easier & faster	• Control selection Problematic • Possibly biased exposure data
Analyses of secular trends	• Can provide rapid answers	• No control of confounding
Case series	• Easy quantitation of incidence	• No control group, so cannot be used for hypothesis testing
Case reports	• Cheap and easy method for generating hypotheses	• Cannot be used for hypothesis testing

Selection of study designs

- Depends on:
  - Research Questions
  - Research Goals
  - Researcher Beliefs and Values
  - Researcher Skills
  - Time and Funds
- It is also related to:
  - Status of existent knowledge
  - Occurrence of disease
  - Duration of latent period
  - Nature and availability of information
  - Available resources

Types of error in **Pharmacoepidemiology** studies

- **Four Possibilities in Testing Whether the Treatments Differ (e.g tt A and B**
  - The treatments do not differ, and we correctly conclude that they do not differ.
  - The treatments do not differ, but we conclude that they do differ.
  - The treatments differ, but we conclude that they do not differ.
  - The treatments do differ, and we correctly conclude that they do differ.

Four possibilities as presented in a 2 × 2 table

		Reality	
		Treatment **are not** different	Treatment are different
Decision	Conclude treatments **are not** different	Correct decision	Type II error (β)
	Conclude treatments are different	Type I error (α)	Correct decision

Types of error in Pharmacoepidemiology studies

- The *probability* that we will make a type I error is designated α
- The *probability* that we will make a type II error is designated β
- α is the so-called *P* value
  - When you see "*P* < .05," the reference is to α.
  - *P* < .05 means we have concluded that therapy A differs from therapy B on the basis of the sample of subjects included in our study, which we found to differ.
  - The probability that such a difference could have arisen by **chance** alone, and that this difference between our groups does not reflect any true difference between therapies A and B, is only .05 (or 1 in 20).

Types of error in Pharmacoepidemiology studies

- When there is a true difference between therapies A and B in realities, there are only two possibilities
  - conclude in error i.e. therapies do not differ (type II error) or β
  - conclude correctly i.e. that the therapies differ.
  - the total of all probabilities = 1
  - the probability of a type II error = β, then the probability that we shall correctly decide on the basis of our study that the therapies differ if there is a difference will equal 1 - β.
  - The probability, 1 - β, is called the *power* of the study.
    - ***`It tells us how good our study is at correctly identifying a difference between the therapies if in reality they are different.***

Assignment

- Review four journals of pharmacoepidemiologic studies done by using the following study design
  - Case report/series
  - Case-control
  - Cohort
  - RCTs
- Interpret the finding
- Identify the strength and weakness of the studies

Concept of Risk and Risk Assessment in Pharmacoepidemiology

- **Ris**k
  - defined as the probability of an event (such as developing a disease) occurring
- **Absolute risk**
  - The incidence of a disease in a population
  - indicate the magnitude of the risk in a group of people with a certain exposure, but because it does not take into consideration the risk of disease in non-exposed individuals, it does not indicate whether the exposure is associated with an increased risk of the disease.
  - Comparison is fundamental to epidemiology.

- Occurrence of disease can be measured using rates or proportions.
- *Rates*
  - tell us how fast the disease is occurring in a population
- *Proportions*
  - tell us what fraction of the population is affected
- Incidence Rate
  - the number of new cases of a disease that occur during a specified period of time in a population at risk for developing the disease.

Incidence Rate per 1000= No. of new cases of a disease occurring in the population during specified period X 1000

No. of persons who are at risk of developing the disease during that period of time

- Prevalence or prevalence rate
  - Proportion of persons in a population who have a particular disease or attribute at a specified point in time or over a specified period of time.
- *Prevalence = all new and pre - existing case*

  $$\frac{\textit{during a given time period}}{\textit{population during the same time period}} \times 10^n$$

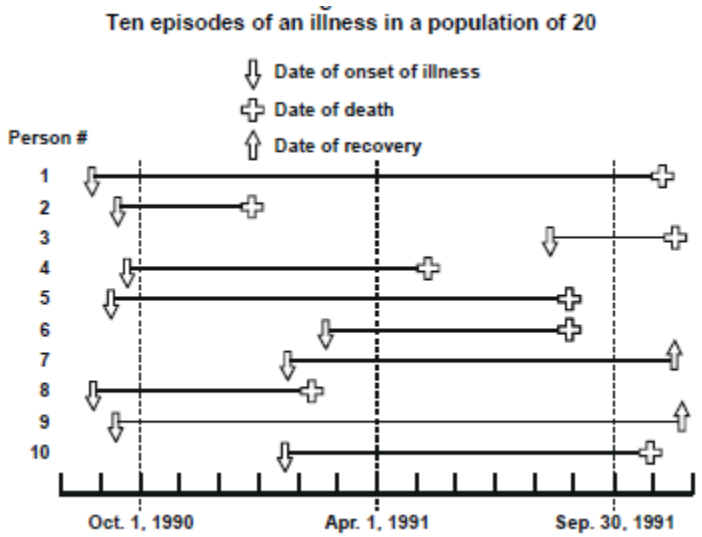
Frequently used measures of morbidity

Measure	Numerator (x)	Denominator (y)	Expressed per Number at Risk(10^n)
Incidence Rate	# new cases of a specified disease reported during a given time interval	average population during time interval	varies: 10^n where n = 2,3,4,5,6
Attack Rate	# new cases of a specified disease reported during an epidemic period	population at start of the epidemic period	varies 10^n where n = 2,3,4,5,6
Secondary Attack Rate	# new cases of a specified disease among contacts of known cases	size of contract population at risk	varies: 10^n where n = 2,3,4,5,6
Point Prevalence	# current cases, new and old, of a specified disease at a given point in time	estimated population at the same point in time	varies: 10^n where n = 2,3,4,5,6
Period Prevalence	# current cases, new and old, of a specified disease identified over a given time interval	estimated population at mid-interval	varies: 10^n where n = 2,3,4,5,6

Example 1

- In 1989, 733,151 new cases of gonorrhea were reported among the United States civilian population. The 1989 mid-year U.S. civilian population was estimated to be 246,552,000. Calculate the 1989 gonorrhea incidence rate for the U.S. civilian population using these data.

Example 2


Ten episodes of an illness in a population of 20
Date of onset of illness
Date of death
Date of recovery
Person #
1
2
3
4
5
6
7
8
9
10
Oct. 1, 1990
Apr. 1, 1991
Sep. 30, 1991

Example 2

- In the above figure,
  - (a). calculate the incidence rate from October 1, 1990 to September 30,1990, using the midpoint population as the denominator
  - (b) Calculate Point prevalence on October 1, 1990
  - (c) Calculate Period prevalence, October 1, 1990 to September 30, 1991

Answer

- Example 1
  - Define *x and y:*
    - *x = new cases of gonorrhea in U.S. civilians during 1989*
    - *y = U.S. civilian population in 1989*
  - Identify *x, y, and* 10_n*: x = 733,151*
    - *y = 246,552,000*
    - $10_n = 10_5 = 100{,}000$
  - Calculate $(x/y) \times 10_n$*:*
    - $(733{,}151 / 246{,}552{,}000) \times 10_5$
    - $.002974 \times 100{,}000 = 297.4$ per 100,000
- or approximately 3 reported cases per 1,000 population in 1989.

- Example 2 (a)
  - x = new cases occurring 10/1/90–9/30/91 = 4
  - y = total population at midpoint = 20 − 2 = 18
  - (x/y) × 10n =
  - (4/18) × 100 = 22/100
  - So the one-year incidence was 22 cases per 100 population

- Example 2 (b)
- Point prevalence on October 1, 1990:
  - x = cases present on 10/1/90 = 6
  - y = population = 20
  - *(x/y) × 10n*
  - *(6/20) × 100 = 30%*

- Attributable Risk Percent
  - It provides an estimate of the **proportion** of the disease among the exposed that is attributable to the exposure.
  - It provides information pertaining to the proportion of the disease in the exposed group that could be **prevented by eliminating** the exposure.

$AR\% = (I_E - I_{NE}/I_E)x\ 100\%$

Attributable Risk for the Total Population—Population Attributable Risk (PAR)

Population Attributable Risk (PAR): Incidence in total population – Incidence in non exposed group

Drug Utilization

Drug Utilization

- **Drug utilization research**
  - Defined as «the **marketing**, **distribution**, **prescription**, and **use** of drugs in a society, with special emphasis on the resulting **medical**, **social** and **economic** consequences»
  - Describes the **extent**, **nature** and **determinants** of drug exposure.

Drug Utilization…..cont'd

- **Drug utilization research**
  - **Descriptive studies**
    - Describe patterns of drug utilization
    - Identify problems deserving more detailed studies.
  - **Analytical studies**
    - link data on drug utilization to figures on morbidity, outcome of treatment and quality of care with the ultimate goal of assessing whether drug therapy is rational or not

Drug Utilization…..cont'd

- Pattern of use
  - covers the extent and profiles of drug use and the trends in drug use and costs over time.
- Quality of use
  - determined using audits to compare actual use to national prescription guidelines or local drug formularies.
    - the choice of drug (compliance with recommended assortment),
    - drug cost (compliance with budgetary recommendations)
    - drug dosage (awareness of inter-individual variations in dose requirements and age-dependence)
    - awareness of DI and ADR
    - the proportion of patients who are aware of or unaware of the costs and benefits of the treatment.

Drug Utilization…..cont'd

- Determinants of use
  - These include **user characteristics** (e.g. socio-demographic parameters and attitudes towards drugs)
  - **prescriber characteristics** (e.g. speciality, education and factors influencing therapeutic decisions) and drug characteristics (e.g. therapeutic properties and affordability).

Drug Utilization…..cont'd

- Outcomes of use
  - These are **the health out comes** (i.e. the benefits and adverse effects) and **the economic consequences**.
- Drug utilization research also provides insight into the **efficiency of drug use**
  - whether a certain drug therapy provides value for money
    - to set priorities for the rational allocation of health care budgets.

Why drug utilization research?

- Description of drug use **patterns**
- Early **signals** of irrational use of drugs
- **Interventions** to improve drug use - follow-up
- **Quality control** of drug use

Description of drug use patterns

- To estimate the numbers of patients exposed to specified drugs within a given time period.
  - **Prevalence vs incidence.**
- To describe the **extent** of use at a certain moment and/or in a certain area (e.g. In a country, region, community or hospital).
  - Continuous evaluation system (patterns are followed over time and trends in drug use can be discerned.

Description of drug use patterns…

- To estimate to what extent drugs are properly used, overused or underused.
- To determine the pattern or profile of drug use and the extent to which alternative drugs are being used to treat particular conditions.
- To compare the observed patterns of drug use for the treatment of a certain disease with current recommendations or guidelines.

Description of drug use patterns…

- As quality indicators to patterns of drug utilization.
  - E.g. DU90% (drug utilization 90%)
  - The number of drugs that account for 90% of drug prescriptions and the adherence to STG
- Drug utilization data can be feedback to prescribers.
  - The drug prescribing by a particular individual can be compared with some form of «gold standard» or best practice, and with the average prescriptions in the relevant country, region or area.

Interventions to improve drug use - follow-up

- The effects of measures taken to ameliorate undesirable patterns of drug use
  - e.g. provision of regional or local formularies
  - Information campaigns
  - Regulatory policies
- The impact of regulatory changes or changes in insurance or reimbursement systems
- The extent to which the promotional activities of the pharmaceutical industry and the educational activities of the society affect the patterns of drug use should be assessed.

Quality control of drug use

- **Step 1. Plan :** Analyze current situation to establish a plan for improvement (
  - e.g. analyze current prescription patterns of individual prescribers
- **Step 2. Do**: Implement the plan on a small scale
  - (e.g. provide feedback on possible overuse
- **Step 4:** Act ; Revise plan or implement plan on large scale (e.g. guide national implementation of plan).
- Step 5: Check Check to see if expected results are obtained (e.g. evaluate whether prescription patterns really improve).

Drug utilization studies and drug policy decisions

- Many of the questions asked in drug utilization research and the answers obtained are important
  - **Initiating and modifying a rational drug policy** at both national and local levels.

Types of drug use information

- Patient information
- Prescriber information
- Drug-based information
  - Level of drug use aggregation
  - Indication
  - Prescribed daily doses .
- Problem or encounter-based information
- Types of drug utilization study
- Drug costs

WHO/INRUD Drug Use Indicators

- Drug use indicators
  - Describe drug use at a given point in time or to monitor changes over time.
  - *Core and supplementary* drug use indicator
  - Developed to measure performance in ***three*** general areas
    - Pharmaceutical ***prescribing practice*** by health provider
    - ***Patient care***, (both consultation and pharmaceutical dispensing)
    - Availability of ***facility specific factors*** which support rational use

WHO/INRUD Drug Use……cont'd

- Core drug use indicator
  - Highly standardized
  - do not need adaptation
  - recommended for inclusion in drug use study using indicators
  - They do not measure all important aspects of drug utilization
  - Provide a simple tool for quickly and reliably assessing a few critical aspects of pharmaceutical health in primary health care

WHO/INRUD Drug Use……cont'd

- Complimentary or supplementary indicator
  - Difficult to measure
  - cannot be collected reliably in some settings.
  - less standardized
    - have to be defined before the indicator can be used depending on local variables

WHO/INRUD Drug Use……cont'd

- Core drug use indicator (12)
  - Prescribing indicator (5)→ retrospective/prospective data
    - Average number of drugs per encounter
    - Percentage of drugs prescribed by generic name
    - Percentage of encounter with an antibiotic prescribed
    - Percentage of encounter with an injection prescribed
    - Percentage of drugs prescribed from EDL or formulary

WHO/INRUD Drug Use……cont'd

- Patient care indicators (5) → Only prospective data
  - Average consultation time
  - Average dispensing time
  - Percentage of drugs actually dispensed
  - Percentage of drugs adequately labeled
  - Patients' knowledge of correct dosage
- Facility indicators (2) → Only prospective data
  - Availability of copy of EDL or formulary
  - Availability of key drugs

WHO/INRUD Drug Use……cont'd

- Complementary drug use indicator (7)
  - Percentage of patients treated without drugs
  - Average drug cost per encounter
  - Percentage of drug costs spent on antibiotics
  - Percentage of drug costs spent on injection
  - Prescription in accordance with treatment guidelines
  - Percentage of patients satisfied with the care they received
  - Percentage of health facilities with access to impartial DInfo.

Core drug use indicator

- **Prescribing indicator**

1. Average number of drugs per encounter
   - Measure degree of *Polypharmacy*
   - Average, calculated by **dividing the total number of different drugs products prescribed, by the number of encounters surveyed.**
   - *It is not relevant weather the patient actually received drugs.*

Core drug use…….cont'd

2. Percentage of drugs prescribed by generic name
   - measure the tendency to *prescribe by generic name*
   - Percentage, calculated by dividing the total the number of drugs prescribed by generic name by the total number of drugs prescribed, multiplied by 100.
3. Percentage of encounter with an antibiotic prescribed

Core drug use…….cont'd

4. Percentage of encounter with an injection prescribed
   - To measure the overall level of use of two important (i.e. antibiotic and injection), but commonly overused and costly forms of drug therapy
   - Percentages, calculated by dividing the number of patient encounter during which an antibiotic or an injection are prescribed, by the total number of encounter surveyed, multiplied by 100.

Core drug use…….cont'd

5. Percentage of drugs prescribed from EDL or formulary
   - measure the degree to which practices conform to a national drug policy, as indicated by prescribing from national essential drugs or formulary for the type of facility surveyed.
   - Percentages, calculated by dividing the number of products prescribed which are listed on the EDL or local formulary (or which are equivalent to drugs on the list) by the total number of products prescribed, multiplied by 100.

Core drug use…….cont'd

- ***Patient care indicators (5)***
  - Average consultation time
    - To measure the time that medical personnel spend with patients in the process of consultation and prescribing.
    - Average, calculated by dividing the total time for series of consultation, by the number of consultations.
  - Average dispensing time
    - To measure the average time that personnel dispensing drugs spend with patients.
    - Average, calculated by dividing the total time for dispensing drugs to a series of patients, by the number of encounters.

Core drug use…….cont'd

– Percentage of drugs actually dispensed

- To measure the degree to which health facilities are able to provide the drugs which were prescribed.
- Percentage, calculated by dividing the number of drugs actually dispensed at the health facility by the total number of drugs prescribed, multiplied by 100.

Core drug use…….cont'd

- Percentage of drugs adequately labeled
  - To measure the degree to which dispensers record essential information on the drug packages they dispense.
  - Percentage, calculated by dividing the number of drug package containing at least *patient name*, *drug name* and *when* the drug should be taken, by the total number of drug packages dispensed, multiplied by 100.

Core drug use…….cont'd

- Patients' knowledge of correct dosage
  - To measure *effectiveness of the information* given to patients on the dosage schedule of the drugs they receive.
  - Percentage, calculated by dividing the number of patients who can adequately report the dosage schedule for all drugs, by the total number of patients interviewed, multiplied by 100.

Core drug use…….cont'd

- ***Facility indicators***
  - Availability of copy of EDL or formulary
    - to indicate the extent to which copies of the NEDL or local formulary are *available* at health facility
    - Yes or no per facility
  - Availability of key drugs
    - To measure the availability at health facilities of *key drugs* recommended for treatment of some common health problems.
    - Percentage, calculated by dividing the number of specified products actually in stock by the total number of drugs on the checklist, multiplied by 100.

Drug-centered and patient-centered approach in drug use studies

- **Drug-based information**
  - trends in total drug use
    - drug use at various levels
    - information on indications, doses and dosage regimens

Level of drug use aggregation

- Example- 1: The relative use of **drug groups** in the treatment of hypertension.
  - aggregate data on ***diuretics***, ***beta-blockers*** and angiotensin-converting enzyme (**ACE**) inhibitors
- Example- 2: the relative use of beta-blockers in hypertension
  - Aggregate data at the substance (generic drug) level
- Example 3: Relative use of **generic** versus **branded** or innovator products.
- Example 4: trend towards use of **higher strengths of antibiotics**
  - Aggregate data on the level of dose strength

Indication

- Example- the relative use of drug groups in treating hypertension
  - E.G 75% of **ACE** inhibitors are used to treat hypertension whereas only 43% of **diuretics** are used for this indication
  - Most of the high-ceiling diuretics used are for treating **heart failure**
- Example - is amoxicillin utilized rationally?
  - Break down data on amoxicillin use into indications and compare these uses with the appropriate guidelines.

Prescribed daily doses

- The prescribed daily dose (PDD)
  - It is the **average daily** dose prescribed, as obtained from a representative sample of prescriptions
- DDD per 1000 inhabitants per day
  - Allows aggregation of data across **drug** groups
  - **Comparisons** between countries, regions and health facilities is possible
- DDD may not reflect the actual PDDs

Prescribed daily doses

- The PDDs differ between
  - countries and ethnic groups
  - areas or health facilities within the
  - Differ for different indications of the same drug

Relative use of antidepressants in Australia in 1998

	Prescription volume (millions)a	% of total prescription volume	DDD/1000 population/day	% of total population/dayDDD/1000
Tricyclics (N06AA)	3.53	48.82	8.40	28.09
SSRI (N06AB)	3.09	42.74	17.20	57.53
Moclobemide (N06AG02)	0.61	8.44	4.3	14.38
Total	7.23	100	29.9	100.0

Prescribed daily doses

- The DDD per 1000 inhabitants per day
  - often used to derive a rough estimate of the prevalence of use in the population being studied,
  - for chronic diseases it may even be used to assess the prevalence of a disease when the drug is prescribed for a single indication.

Drug classification systems

- A drug classification system
  - a **common language** for describing the drug assortment in a country or region
  - It is a prerequisite for national and international **comparisons** of drug utilization data, which have to be collected and aggregated in a uniform way.
- Access to standardized and validated information on drug use
  - allow **audits of patterns** of drug utilization
  - identify **problems** in drug use
  - initiate educational or other **interventions**
  - monitor the **outcomes** of these interventions.
- The main purpose of having an international standard
  - is to be able to compare data between countries

Drug classification systems…

- Drugs can be classified in different ways according to:
  - their mode of action
  - their indications
  - their chemical structure
- Each classification system
  - Have its advantages and limitations
- its usefulness will depend on
  - the purpose, the setting used and the user's knowledge of the methodology.

Drug classification systems…

- The two commonest one are
  - Anatomical Therapeutic (AT) classification
    - Developed by the European Pharmaceutical Market Research Association (EPhMRA)
  - Anatomical Therapeutic Chemical (ATC) classification
    - developed by Norwegian researchers

Drug classification systems…

- In the EPhMRA system
  - drugs are classified in groups at three or four different levels.
- The ATC classification system
  - modifies and extends the EPhMRA system to include
  - fourth level - a therapeutic/ pharmacological/chemical subgroup as the
  - fifth level - chemical substance

Drug classification systems…

- The ATC classification
  - basis for the classification of ADR used by the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden
  - a tool for presenting drug utilization statistics
  - and it is recommended by WHO for use in international comparisons

Drug classification systems…

- The ATC classification system
  - divides the drugs into different groups
    - **organ** or system on which the drugs act
    - Chemical
    - pharmacological
    - therapeutic properties.
- Drugs are classified in groups at five different levels
  - (first level)14 main groups
  - (second and third levels).two therapeutic/pharmacological subgroups
  - The fourth level is a therapeutic/pharmacological/chemical subgroup
  - the fifth level is the chemical substance.

Drug classification systems

- Example ATC classification of glibenclamide
  - A Alimentary tract and metabolism
    - (first level, main anatomical group)
  - A10 Drugs used in diabetes
    - (second level, main therapeutic group)
  - A10B Oral blood-glucose-lowering drugs
    - (third level, therapeutic/pharmacological subgroup)
  - A10B B Sulfonamides, urea derivatives
    - (fourth level, chemical/therapeutic/pharmacological subgroup)
  - A10B B01 Glibenclamide
    - (fifth level, subgroup for chemical substance

Drug classification systems

- A medicinal product can be given more than one ATC code
  - if it is available in **two or more strengths** or formulations with clearly **different therapeutic** uses.
- Example - Bromocriptine
  - The low-dose tablets are used as prolactin inhibitors
    - classified in G02 – Other gynaecologicals
  - The higher dose are used to treat Parkinson disease
    - classified in N04 - Anti-Parkinson drugs.

Drug classification systems

- Different formulations with different indications
  - given separate ATC codes, for
- example prednisolone is given several ATC
  - A07EA01 Intestinal antiinflammatory agents (enemas and foams)
  - C05AA04 Antihemorrhoidals for topical use (suppositories)
  - D07AA03 Dermatological preparations (creams, ointments and lotions)
  - H02AB06 Corticosteroids for systemic use (tablets, injections)
  - R01AD02 Nasal decongestants (nasal sprays/drops)
  - S01BA04 Ophthalmologicals (eye drops)
  - S02BA03 Otologicals (ear drops)

Drug classification systems

- The purpose of the ATC/DDD system
  - To serve as a tool for drug utilization research in order to improve quality of drug use
  - To present and compare drug consumption statistics at international and other levels

The concept of the defined daily dose (DDD)

- The DDD
  - is the assumed average maintenance dose per day for a drug used for its main indication in adults.
  - a unit of measurement
  - does not necessarily correspond to the recommended or prescribed daily dose (PDD)
    - Doses - based on individual characteristics (e.g. age and weight) and pharmacokinetic considerations.
  - is often a compromise based on a review of the available information about doses used in various countries
  - may even be a dose that is seldom prescribed, because it is an average of two or more commonly used dose sizes.

DDD…

- Drug utilization figures should ideally be presented
  - as numbers of DDDs per 1000 inhabitants per day
    - For anti-infective or drugs used for short periods
  - as DDDs per 100 bed-days for inpatients
    - when drug use by inpatients is considered

Defined daily dose (DDD)

- *DDDs per 1000 inhabitants per day*
  - Example: 10 DDDs per 1000 inhabitants per day
  - Means 1% of the population on average might receive a certain drug or group of drugs daily.
- *DDDs per 100 bed-days*
  - example, 70 DDDs per 100 beddays of hypnotics provide
  - 70% of the inpatients might receive a DDD of a hypnotic every day.

Defined daily dose (DDD)

- *DDDs per inhabitant per year*
  - gives an estimate of the average number of days for which each inhabitant is treated annually.
  - example, 5 DDDs per inhabitant per year indicates that the utilization is equivalent to the treatment of every inhabitant with a five-day course during a certain year.

Prescribed daily dose and consumed daily dose

- PDD
  - important to relate to diagnosis on which the dosage is based.
  - gives the average daily amount of a drug that is actually prescribed.
  - It does not necessarily reflect actual drug utilization.
  - Some prescribed medications are not dispensed, and the patient does not always take all the medications that are dispensed.

Social aspects of drug use

- Compliance, adherence and concordance
  - Compliance
    - 'The extent to which the patient's behaviour matches the prescriber's recommendations.'
- Adherence
  - 'The extent to which the patient's behaviour matches agreed recommendations from the prescriber.'
- Concordance
  - is a relatively recent term, predominantly used in the United Kingdom (UK).
  - doctor and patient agree therapeutic decisions stretches from prescribing communication to patient support in medicine taking.